TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35.U.S.C. 371

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U.S. APPLICATION NO.
09/463851

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB98/02317	31 July 1998 (31/07/98)	31 July 1997 (31/07/97)

TITLE OF INVENTION
PHARMACEUTICAL COMPOUNDS ISOLATED FROM ARISTOLOCHIA TALISCANA

APPLICANT(S) FOR DO/EO/US
ACHENBACH, Hans

Applicant herewith submits to the United States Designated /Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(I).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information:
    1. FORM PCT/ISA/210 (INTERNATIONAL SEARCH REPORT)
    2. FORM PCT/IB/332 (INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION)
    3. FORM PCT/IB/308 (NOTIFICATION OF INTERNATIONAL APPLICATION TO DESIGNATED OFFICES)
    4. FORM PCT/IB/306 (NOTICIFICATION OF THE RECORDING OF A CHANGE)
    5. FORM PCT/RO/101 (PCT REQUEST)
    6. Check in the amount $1,392.00.
    7. Postcard.

09/463851

5.TERNATIONAL APPLICATION NO.	=NTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB98/02317	31 JULY 1998 (31/07/98)	31 JULY 1997 (31/07/97)

514 Rec'd PCT/PTO 31 JAN 2000

17. [X] The following fees are submitted:

CALCULATIONS PTO USE ONLY

Basic National Fee (37 CFR 1.492(a)(1)-(5): Search Report has been prepared by the EPO or JPO $930.00

International preliminary examination fee paid to USPTO (37 CFR 1.482) $720.00

No international preliminary examination fee paid to USTPO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $790.00

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $970.00

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) ..... $ 98.00

ENTER APPROPRIATE BASIC FEE AMOUNT =	$970.00	
Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 C.F.R. 1.492(e)).	$-0-	

Claims	Number Filed	Number Extra	Rate		
Total Claims	29-20=	9	X 18	$162.00	
Independent Claims	2-3=	0	X 82.00	$-0-	
Multiple dependent claim(s) (if applicable)			+ $260.00	$260.00	
TOTAL OF ABOVE CALCULATIONS =				$1392.00	
Reduction by ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$-0-	
SUBTOTAL =				$1392.00	
Processing fee of $130.00 for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$-0-	
TOTAL NATIONAL FEE =				$1392.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$-0-	
TOTAL FEES ENCLOSED =				$1392.00	
				Amt.refunded	$-0-
				charged	$-0-

a. [X] A check in the amount of $ 1392.00 to cover the above fees is enclosed.
b. [ ] Please charge our Deposit Account No. in amount of $___ to cover the above fees. A copy of this sheet is enclosed.
c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-4377. A copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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Reg. No. 32,300

Date: 31 JAN. 2000 (31/01/2000)

EJ US	JAN 2000 (31/01/2000)
Express Mail mailing number	Date of Deposit
I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Assistant Commissioner for Patents, Washington, D.C. 20231	
	LEROY CHICK
Signature of person mailing correspondence	Typed or printed name of person mailing correspondence

PHARMACEUTICAL COMPOUNDS ISOLATED FROM ARISTOLOCHIA TALISCANA

FIELD OF THE INVENTION

This invention relates to compounds derived from the plant *Aristolochia taliscana* and their analogues, and the uses of such compounds in medicine.

BACKGROUND OF THE INVENTION

Aristolochia taliscana, a climbing shrub found in the jungles of the southern coastal region of Mexico, is part of a family of climbing herbs and shrubs called *Aristolochiaceae*, numbering about six hundred species divided into eleven genera, and found mostly in tropical and sub-tropical regions. It is believed that the species *Aristolochia taliscana* is found only in Mexico.

Members of the *Aristolochiaceae* are known for their ability to synthesise phenanthrene alkaloids, and in particular the aristolactam alkaloids and the aristolochic acids, and arylpropanoid compounds such as the lignans and neolignans. Such compounds are disclosed in, for example, R. Hegnauer "Chemotaxonomie der Pflanzen", Vol. III, pp 184-199, Birkhäuser Verlag, Basel und Stuttgart, 1964; R. Hegnauer "Chemotaxonomie der pflanzen", Vol. VII, pp 75-83, Birkhäuser Verlag, Basel - Boston - Berlin, 1989 and F.E. Correa *et al.*"Especies Vegetales Promisorios", Vol. I, pp 440-469, Secretaria Ejecutiva del Convenio Andies Bello (SECAB), Bogota D.E. 1989, Colombia and Lopes *et al.* Rev. Latinoam. Quim.,19 (3-4), 113-17, 1988. In Lopes *et al.*, for example, the isolation of lignans from a number of different *Aristolochiaceae* is described and it is disclosed that such compounds are reported as having anti-tumour, antifungal, antibacterial and insecticidal activity. In Hinou *et al.*, J. Crude Drug Research, 1990, 28(2), 149-51, it is disclosed that aristolactam and aristolochic acid compounds isolated from *Aristolochia longa* have antibacterial activity and cytotoxic activity against P-388 lymphocytic leukaemia and human bronchial epidermoid carcinoma cells.

The isolation and characterisation of lignans, neolignans and related compounds from a wide variety of plant species has been reviewed in a series of articles by R.S. Ward, see for example Natural Product Reports, 1985, Vol. 5 pp 203-206; 1990, Vol. 7, pp 356-363; 1993, Vol. 10, pp 1-23.

However, it is clear from the available literature that the chemical structures and concentrations of arylpropanoid compounds found in *Aristolochiaceae* vary widely from one species to another. For example, in Lopes *et al.* (*idem.*), reference is made to the extraction of four Brazilian species of *Aristolochiaceae*, from which a number of dibenzyl-butyrolactone type lignans and furofuran type lignans were isolated. From studies made by the present inventors, such compounds would appear to be absent from *Aristolochia taliscana*.

Much of the work carried out on the *Aristolochiaceae* has focused on the phenanthrene alkaloid content, and in particular the aristolactam alkaloids found in the plants - see for example Crohare *et al.* Phytochemistry, 1974, Vol. 13, 1957-1962, Priestap, Phytochemistry, 1985, Vol. 24, 849-852, Talapatra *et al.* Phytochemistry, 1988, Vol. 27, 903-906 and Houghton *et al.* Phytochemistry, 1991, Vol. 10, 253-254. Houghton *et al.* suggest that compounds such as aristolochic acid, the ring-opened form of aristolactam, are of interest as immunostimulants and anticancer agents.

Crude extracts from *Aristolochia taliscana* have been known for many years to have certain medicinal properties. A book published in the 1800's, called "Las Plantas Medicinales de Mexico" (Medicinal Plants of Mexico) makes reference to the use of *Aristolochia taliscana* extracts in the treatment of snake bites and it would appear that the native tribes in this region of Mexico have known about the uses of the extracts for many centuries.

In US Patent No. 4782077 it is disclosed that an alkaloid (referred to as taliscanin) extracted from the root of *Aristolochia taliscana*, alleviates the symptoms of Parkinsonism and related neurological disorders. It is also indicated in US 4782077 that the alkaloid taliscanin may be useful in the treatment of various other neurological disorders, including Alzheimer's disease, impotency, and neurological

disorders associated with viral, bacterial, fungal and parasitic infections.

In US 4782077, an extract was prepared by pulverising *Aristolochia taliscana* root and subjecting the powder to soxhlet extraction with hexane and then benzene followed by column chromatography on an alumina column eluting with benzene-ether mixtures. The known aristolactam alkaloid taliscanin, was characterised on the basis of its melting point (272°-273°C) and its spectroscopic data.

However, the aristolactam alkaloid taliscanin has since been tested for its ability to interact with neurotransmitter receptors, and, somewhat surprisingly, exhibited 50% inhibition in only one receptor (the opiate mu receptor) out of twenty seven common receptor types tested, and exhibited very poor levels of inhibition with the remaining receptors. In particular, taliscanin exhibited negligible activity at the dopamine, GABA and serotonin receptors. These results suggest either that taliscanine exerts its neurological effects by a mechanism which is of a currently unknown type (which seems unlikely) or, perhaps, that there is another active principle in *Aristolochia taliscana* which is responsible for the reported activities.

SUMMARY OF THE INVENTION

The present applicants have been able to separate and identify the components of *Aristolochia taliscana* extracts and have found that the extract contains a substantial number of compounds other than aristolactams, in particular certain benzofuran neolignans, many of which are novel. Compounds found in the extracts have been found to have biological properties indicative of therapeutic utility. For example, benzofuran compounds isolated from taliscanine have been tested and have been found to be active as anti-mutagenic agents, as cytotoxic agents, and some have been found to have good antifungal activity. On this basis, it is anticipated that the compounds in question will find use in the treatment of tumours and other neoplastic diseases, as well as fungal infections.

Accordingly, in a first aspect, the invention provides the use of an extract of *Aristolochia taliscana* or one or more anti-mutagenically active components

isolable therefrom for the manufacture of a medicament for the treatment of disease states mediated by mutagenesis.

The invention also provides the use of an extract of an *Aristolochia* species, preferably *Aristolochia taliscana* or one or more component compounds isolable therefrom, for the manufacture of a medicament for the treatment of chronic inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, synovitis and psoriasis.

As indicated above, component compounds of *Aristolochia taliscana* have also been found to have good antifungal activity, and in a still further aspect, the invention provides the use of an extract of *Aristolochia taliscana* or one or more antifungally active compounds isolable therefrom for the manufacture of a composition for antifungal use, for example in the treatment of plants or animals.

The invention also provides pharmaceutical compositions comprising benzofuran compounds of the type found in *Aristolochia taliscana* or benzofuran compounds analogous thereto, for example benzofuran compounds in which an aryl ring (such as an oxygenated phenyl ring) is attached to the heterocyclic ring of the benzofuran, and the uses of such compounds in medicine.

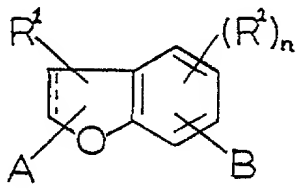
The invention also provides a novel group of benzofuran compounds having an oxygenated aryl ring (such as an oxygenated phenyl ring) attached to the heterocyclic ring of the benzofuran.

DESCRIPTION OF PREFERRED EMBODIMENTS

Compounds for use in Medicine - New Medical Uses of Known and Novel Compounds

In one preferred aspect, the invention provides the use of a compound for the manufacture of a medicament for use in any one or more of the therapeutic uses selected from the treatment of neoplastic diseases or diseases mediated or initiated by mutagenesis or abnormal cellular proliferation, or as a cytotoxic agent, or the treatment of chronic inflammatory conditions; the compound being of the

formula (I):



(I)

wherein the dotted line signifies a single or double bond; n is 0, 1, 2 or 3; A is a monocyclic aryl ring containing up to two heteroatoms and being optionally substituted by one or more substituent groups which may be the same or different and are selected from R^3O, R^3, R^3S, halogen; aryl and heteroaryl, wherein R^3 is hydrogen, or a hydrocarbyl group optionally substituted by a hydroxy or hydrocarbyloxy group; B is selected from carboxy, carboxaldehyde, hydrocarbyl and hydrocarbyloxy groups wherein the hydrocarbyl group is acyclic or cyclic, and optionally contains one or more heteroatoms, and is optionally substituted by one or more hydroxy, alkoxy, alkenyloxy, alkynyloxy, aryloxy, aldehyde, alkanoyl, acetal, hemiacetal and carboxy groups; R^1 is hydrogen or a hydrocarbyl group optionally including one or more heteroatoms and optionally substituted by one or more substituents selected from hydroxy, hydrocarbyloxy and aryl groups; and R^2 is hydroxy or a hydrocarbyl or hydrocarbyloxy group optionally substituted by one or more substituents selected from hydroxy, hydrocarbyloxy and aryl groups.

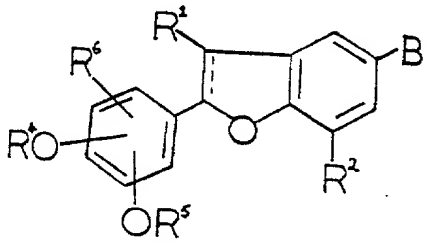
It is preferred that the monocyclic aryl ring A is attached to the 2-position of the furan ring, and it is particularly preferred that the aryl ring is a phenyl group. The phenyl ring can contain up to five substituent groups but preferably contains no more than three substituents.

Preferably, the group B is attached to the 5-position of the benzofuran group.

Preferably, there is only one group R^2, which is attached to the 7-position of the benzofuran ring.

Preferably, the dotted line signifies a double bond.

In a particularly preferred embodiment, the invention provides the use of a compound for the manufacture of a medicament for use in the treatment of the conditions described above in relation to formula (I), the compound having the formula (II):



(II)

wherein the dotted line signifies a single or double bond, B, R^1 and R^2 are as hereinbefore defined, R^4 and R^5 are the same or different and each is selected from hydrogen, C_{1-20} hydrocarbyl, C_{5-20} aryl, or C_{5-20} oxygen-containing heteroaryl; R^6 is selected from hydrogen, halogen, C_{1-20} hydrocarbyl or C_{1-20} hydrocarbyloxy optionally substituted by one or more hydroxy, alkoxy or aralkyloxy groups; or R^6 is C_{5-25} aryl or oxygen or nitrogen-containing heteroaryl.

One preferred group of compounds are the compounds in which B is C_{1-6} alkyl or alkenyl optionally substituted by one or more substituents selected from hydroxy, CHO, or R^7O wherein R^7 is a C_{1-6} alkyl or alkenyl group. More preferably, the group B is selected from $CH=CHCH_3$, $CH_2CH=CH_2$, $CH(OH)CH=CH_2$, $CH=CHCHO$, CHO, $CH=CHCH_2OH$ and $CH(OH)CH(OH)CH_3$. A particularly preferred group B is $CH=CHCH_3$.

In compounds of the formula (II) R^4 and R^5 are preferably selected from hydrogen, or C_{1-6} alkyl, or R^4 and R^5 together define an alkylene group such as $-CH_2-$. Preferably, at least one of R^4 and R^5 is hydrogen.

Particularly preferred compounds are those in which the dotted line signifies a double bond and one of R^4 and R^5 is hydrogen.

Examples of groups R^6 are hydrogen, halogen (e.g. fluoro, chloro, bromo or

iodo), C_{1-6} alkoxy (e.g. methoxy), a 2-benzofuranyl ring, or an aristolactam group.

In the foregoing formulae (I) and (II), examples of hydrocarbyl groups are aliphatic, alicyclic and aromatic groups such as alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, cycloalkenyl, cycloalkenylalkyl, cycloalkenylalkenyl, aryl, aralkyl, aralkenyl, aralkynyl. The hydrocarbyl groups can be optionally interrupted by one or more heteroatoms such as oxygen and sulphur.

Particular examples of alkyl groups are C_{1-6} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl.

Examples of cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicycloheptanyl, decalinyl, adamantyl, norbornyl and bicyclooctyl.

Examples of alkenyl and alkynyl groups include vinyl, ethynyl, allyl, 1-propenyl, propargyl, but-1-enyl, but-2-enyl, but-3-enyl and 3-methylbutenyl.

Examples of cycloalkenyl groups are cyclopentenyl, cyclohexenyl, cycloheptenyl, and monocyclic, bicyclic and tricyclic terpene groups.

Examples of aryl groups are phenyl and naphthyl.

Examples of phenylalkyl and phenylalkenyl groups are benzyl, phenethyl, phenylpropyl, phenylbutyl and styryl groups.

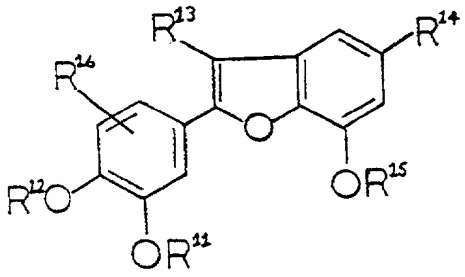
<u>First Medical Uses of Compounds Not Previously Disclosed As Having Therapeutic Utility</u>

Many compounds of the formulae (I) and (II) have not previously been disclosed as having any therapeutic uses. Accordingly, in another embodiment, the invention provides a compound of the formula (I) or (II) as hereinbefore defined for use in medicine, for example for use in any one or more of the therapeutic uses selected from the treatment of neoplastic diseases or diseases mediated or initiated by mutagenesis or abnormal cellular proliferation, or as a cytotoxic agent, or the

treatment of chronic inflammatory conditions, or as an anti-fungal agent in the treatment of plants or animals; but provided that when R^1 is 3-methyl, R^2 is a single methoxy group at the 7-position, and either (i) the furan ring is unsaturated and is substituted at the 2-position with a 4-hydroxy-3-methoxyphenyl group or a 3,4-methylenedioxyphenyl group; or (ii) the furan ring is a 2,3-dihydrofuran ring and is substituted at the 2-position with a 4-hydroxy-3-methoxyphenyl group, then B is other than a prop-1-enyl group attached to the 5-position of the benzfuran ring.

Novel Compounds *per se*

The present invention also provides novel compounds *per se* of the formula (III):



wherein R^{11} is hydrogen or C_{1-6} alkyl;

R^{12} is selected from hydrogen, C_{1-6} alkyl; a cyclic terpenoid group or a group of the formula E, G or J;

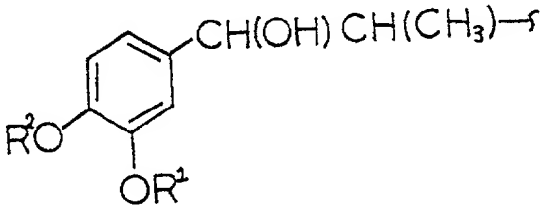
R^{13} is selected from hydrogen; C_{1-3} alkyl or hydroxy-C_{1-3} alkyl;

R^{14} is selected from CH=CH-CH_3, CH(OH)CH=CH_2, CH=CH-CHO, CH=CH-CH_2OH, CH(OH)CH(OR^{17})CH_3, or a group L;

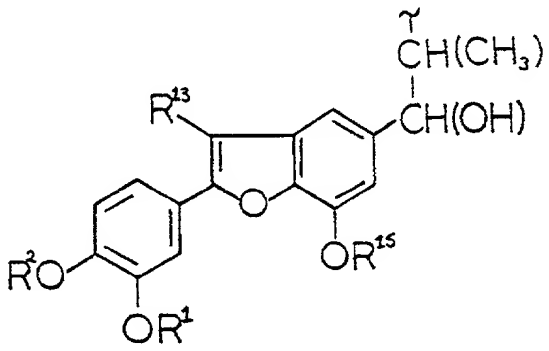
R^{15} is hydrogen or C_{1-6} alkyl;

R^{16} is hydrogen, a group M or an aristolactam group; and

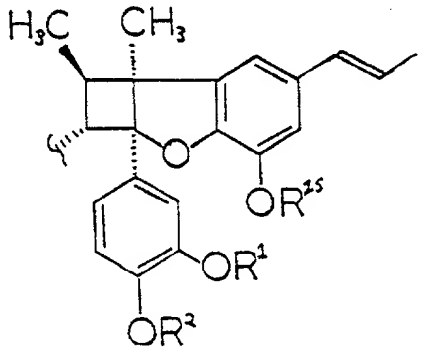
R^{17} is hydrogen or a group T; wherein the groups E, G, L, J, M and T are represented by the formulae:



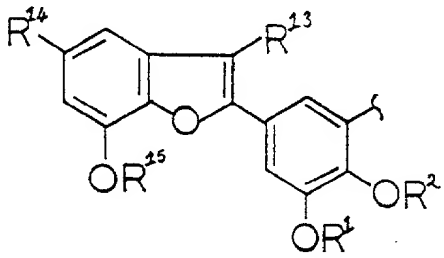
(E)



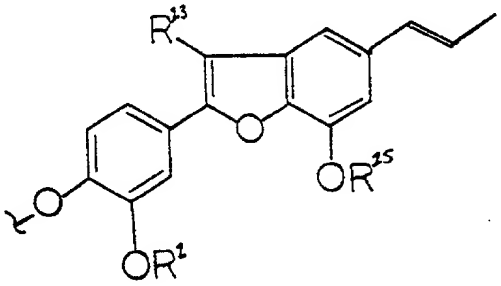
(G)



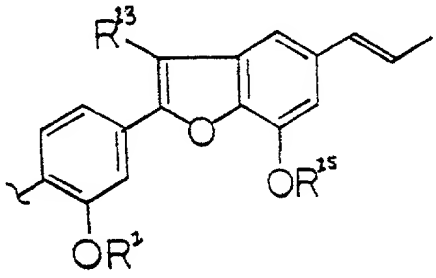
(L)



(J)



(M)

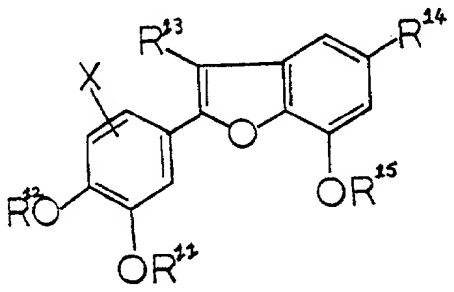


(T)

and pharmaceutically acceptable salts thereof; provided that when R^{11}, R^{13} and R^{15} are all methyl,and R^{12} and R^{16} are both hydrogen, R^{14} is selected only from $CH(OH)CH=CH_2$, $CH=CH\text{-}CHO$, $CH=CH\text{-}CH_2OH$, $CH(OH)CH(OR^{17})CH_3$ where R^{17} is a group T, or a group L.

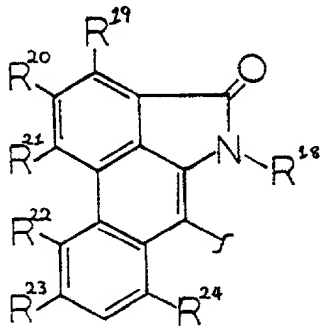
In one particular embodiment, there is provided a novel compound of the

formula (IV):



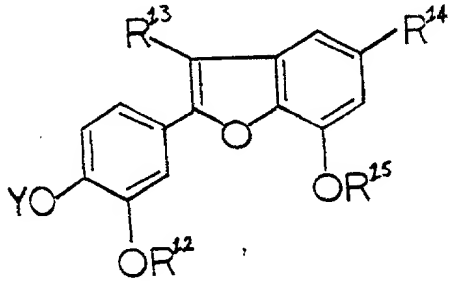
(IV)

wherein R^{11}, R^{12}, R^{13} R^{14}, R^{15} and R^{17} are as hereinbefore defined and X is a group:



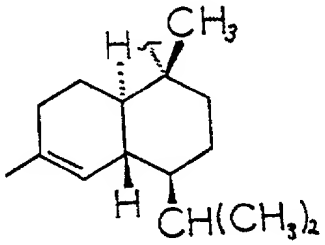
wherein R^{18} is hydrogen, benzyl or C_{1-6} alkyl; R^{19} to R^{24} are the same or different and are selected from hydrogen, hydroxy, C_{1-6} alkoxy, C_{1-6} alkyl and hydroxy-C_{1-6} alkyl; or any two adjacent groups together form an alkylene dioxy group.

In another embodiment, the invention provides novel compounds of the formula (V):



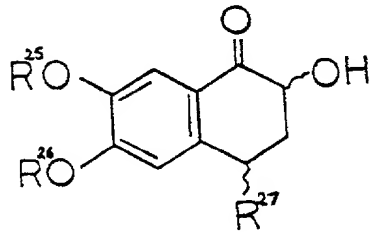
(V)

wherein Y is a monocyclic or bicyclic terpenoid group and in particular a group of the structure:



Tetralone Compounds

In a further aspect, the invention provides tetralone compounds for use in medicine, the tetralone compounds being of the formula (VI):



wherein R^{25} and R^{27} are the same or different and each is C_{1-6} alkyl, or R^{25} and R^{26} together form an alkylene group (such as methylene); and R^{26} is hydrogen or C_{1-6} alkyl.

Preferably R^{25}, R^{26} and R^{27} are all methyl.

Tetralone compounds of the formula (VI) have biocidal activity, and in particular cytotoxic, antibacterial and antifungal activity. It is therefore anticipated that they will be useful in the treatment of proliferative and infective diseases and conditions such as cancers and bacterial and fungal infections.

Accordingly, the invention also provides a compound of the formula (VI) for use in the treatment of bacterial or fungal infections, or for use in the treatment of cancers and other proliferative diseases such as psoriasis.

Compounds of the formula (VI) have previously been reported as synthetic intermediates (see Ioie *et al.* Chem. Pharm. Bull. 38, 1851-56 (1990).

Particular novel compounds of the invention are:
(±)-5-(1-Hydroxyallyl)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran (**Compound 9**);
2-(4-Hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-5-(E)-propenylbenzofuran (**Compound 10**);
2-(4-Hydroxy-3-methoxyphenyl)-7-methoxy-3-methyl-5-[(E)-3-oxopropenyl]benzofuran (**Compound 11**);
5-Formyl-3-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran (**Compound 12**);
2-(4-Hydroxy-2-methoxyphenyl)-5-[(E)-3-hydroxypropenyl]-7-methoxy-3-methylbenzofuran (**Compound 13**);
2-(3,4-Dihydroxyphenyl)-7-methoxy-3-methyl-5-(E)-propenylbenzofuran (**Compound 14**);
erythro-5-(1,2-Dihydroxypropyl)- 2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran (**Compound 15**);
(2R,3R)-2,3-Dihydro-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-5-(E)-propenylbenzofuran (**Compound 19**);
erythro-1-(4-Acetoxy-3-methoxyphenyl)-2-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propylacetate (**Compound 22**);
threo-1-(4-Acetoxy-3-methoxyphenyl)-2-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propyl-acetate (**Compound 23**);
threo-1-[2-(4-Hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran-5-yl]-2-[4-(3-methyl-5-(e)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propan-1-ol (**Compound 24**);
2-Methoxy-4-[7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl]-6-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]phenol (Compound 25)
8.2',9.3'-Tetrahydro-bis-eupomatenoid-7 (**Compound 26**);
15-(Aristolactam-I-9-yl)-eupomatenoid-7 (**Compound 27**);
14-O-α-Cadinyl-eupomatenoid-7 (**Compound 28**); and
(2R,4S)-2-Hydroxy-6-methoxy-4,7-dimethyl-1-tetralone (**Compound 34**).

Extraction of Compounds From *Aristolochia taliscana*

Certain compounds of the formulae I to VI can be obtained by solvent extraction of plant material, such as roots, bark, leaves and twigs, from *Aristolochia taliscana* using solvents such as benzene followed by chromatographic separation of the components of the solvent extract. A typical extraction protocol is described in detail below.

Synthesis of Compounds of the Formulae I to V

The compounds of the invention, whether naturally occurring or synthetic analogues thereof can be synthesized from readily available starting materials by synthetic methods well known to those skilled in the art.

For example, compounds of the formulae (I) or (II) can be prepared by means of the reaction scheme set out in Figure 1.

The reaction conditions and reagents employed in the scheme set out in Figure 1 can be substantially as described in M. Watanabe *et al.* Chem. Pharm. Bull. 37, 2884 (1989); *ibid.* 38, 41 (1990), and *ibid.* 39, 3123 (1991), the contents of which are incorporated herein by reference.

An alternative synthetic scheme applicable to compounds of the formulae (I) or (II) wherein R^1 is a methyl group attached to the 3-position of the furan ring and A is an aryl group attached to the 2-position of the furan ring, is set out in Figure 2.

In the reaction scheme shown in Figure 2, the methoxymethylaryl ketone is reacted with the substituted *o*-hydroxybenzaldehyde in an acidic medium (for example a mixture of hydrochloric acid and acetic acid) to give a benzpyryllium salt which is then subjected to oxidation and rearrangement in the presence of hydrogen peroxide and methanol at pH 5.8 to give a benzfuran 3-carboxy ester. The benzfuran 3-carboxyester can then be treated successively with (i) lithium aluminium hydride in an ether such as diethyl ether; (ii) manganese dioxide in a non-

polar solvent such as benzene; (iii) 1,2 ethylene-dithiol, acetic acid and boron trifluoride etherate; and (iv) Raney nickel in an alcohol such as ethanol. The general conditions under which each of the above reactions can be carried out are disclosed in McCredie *et al.*, Austral. J. Chem. 22, 1011 (1969), the contents of which are incorporated herein by reference.

Pharmaceutical Uses

The extracts and compounds of the invention are useful in a number of medical aspects. In use as therapeutic agents, the compounds or extracts can be administered in standard manner, for example orally, parenterally, transdermally, rectally, via inhalation or via buccal administration. Preferably, however, they are administered orally. The dosage employed will depend on the nature and purity of the extract and the concentrations of the active principles. For an extract that has not been fractionated, the concentration administered can be in the range from 0.5mg to 500mg (dry weight) of extract per patient per day, more usually 1mg to 100mg per day. If an isolated compound or synthetic analogue thereof, or mixture of such compounds is employed, the dosages of such compounds administered typically will be similarly in the range 0.5mg to 500mg per patient per day, more usually 1mg to 100mg per day. The extracts or compounds may be administered as single doses or multiple doses as desired. The dosages of the extracts or compounds of the invention administered will depend upon *inter alia* the potency of the extract or compound, and the nature and severity of the disease state or condition under treatment but ultimately, however, will be at the discretion of the physician.

Pharmaceutical Formulations

The extracts and compounds of the invention can be formulated as solutions, syrups, tablets, capsules, lozenges, inserts, patches, powders, pills, solutions for injection or drops, or aerosols such as dry powder aerosols or liquid aerosols, by way of example. Such formulations can be prepared in accordance with methods well known *per se*.

In a particular embodiment, the compositions of the invention can take the

form of solid or semi-solid unit dosage form. For example, the compositions can take the form of tablets, granules, lozenges or capsules.

A solid or semi-solid dosage form according to the present invention can contain, for example, from 10mg to 1000mg of the extract or compounds of the invention, more typically 50mg to 500mg, e.g. 100mg to 400mg, and in particular 150mg to 350mg, particular unit dosages being approximately 200mg and 300mg.

A tablet composition will typically contain one or more pharmaceutically acceptable solid diluents, examples of which include sugars such as sucrose and lactose, and sugar alcohols such as xylitol, sorbitol and mannitol; lactose and sorbitol being particular examples.

The tablets will also typically contain one or more excipients selected from granulating agents, binders, lubricants and disintegrating agents.

Examples of disintegrants include starch and starch derivatives, and other swellable polymers, for example cross-linked polymeric disintegrants such as cross-linked carboxymethylcellulose, cross-linked polyvinylpyrrolidone and starch glycolates.

Examples of lubricants include stearates such magnesium stearate and stearic acid.

A capsule composition typically will comprise an outer shell or casing which may, for example, be formed from hard or soft forms of gelatin or gelatin-equivalents in conventional fashion. The outer shell is filled with an extract or a compound in accordance with the invention. The capsule filling may be in the form of a powder, or granules, or beads, or may be in the form of a liquid or semi-solid. Where the mixture is in the form of granules, the granules can consist of the extract or compound of the invention alone, or granulated together with a granulating agent, or they can additionally comprise a solid diluent, for example of the type set forth above.

The granules can be wet granulated or dry granulated as desired.

When the capsule filling is in liquid or semi-solid form, the extract or compound can be dissolved or suspended in a semi-solid carrier material such as a polyethylene glycol or a liquid carrier such as a glycol, e.g. propylene glycol, or glycerol. In general, it is preferred that the capsule is in solid or semi-solid form when hard gelatin capsules are used; liquid or semi-solid forms being preferred with soft gelatin capsules.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention will now be illustrated, but not limited, by reference to the following examples.

GENERAL EXPERIMENTAL DETAILS AND ISOLATION PROCEDURE

General

In the following examples, all melting points are uncorrected. Analytical thin layer chromatography (TLC) was performed on precoated plates (HPTLC plates, silica gel 50 F_{254}, Merck) using the following systems: S-1 = $CHCl_3$-MeOH (99:1), S-2 = $CHCl_3$-MeOH (96:4), S-3 = cyclohexane-EtOAc (1:1); detection: UV, anisaldehyde reagent [E. Stahl, and U. Kaltenback, Journal of Chromatography, 1961, 5, 351].

Unless otherwise stated, the optical properties and UV and IR spectra were recorded as follows: $[\alpha]_D$ in $CHCl_3$ at 20°, CD and UV in MeOH, IR in $CHCl_3$.

Unless otherwise stated, ^1H NMR were run at 360 MHz and ^{13}C NMR at 90 MHz in $CDCl_3$ with TMS as internal standard.

EIMA were obtained at 70 eV; DCIMS with NH_3 or isobutane, respectively. Apart from key ions, the only ions listed are those with relative intensities >10% and m/z >100.

Column chromatography (CC) and medium pressure liquid chromatography

(MPLC) were carried out on silica gel 60 (Macherey-Nagel) and on LiChroprep® RP 18 (40-60 μm, Merck). For CC, Fractogel PVA 500 (Merck), and Fractogel TSK HW-40 (S) (Merck) were also used.

High pressure liquid chromatography (HPLC) was performed on LiChrosorb RP 18 (7 μm, Merck).

Plant material

Roots of *Aristolochia taliscana* Hook (Aristolochiaceae) were collected by Jorge Pérez de la Rosa (Instituto Tecnologico y de Estudios Superiores de Monterrey, ITESM) from Colima (Mexico) and identified by Prof. H. Sánchez. A voucher specimen is held at the Universidad de Guadalajara, Instituto de Botanica, Guadalajara (Mexico).

EXAMPLE 1

Extraction and isolation of the Components of *Aristolochia taliscana*

Air dried, pulverized roots and rhizomes (3.5kg) of *Aristolochia taliscana* were extracted with benzene at room temperature to give 16g of a red-brown extract after removal of solvent. This extract was separated by column chromatography on Fractogel TSK HW 40 (S) with methanol to give 10 fractions (designated **A.t.1** to **A.t 10**), which were then subjected to further chromatographic separation by repeated MPLC or CC using the following systems (a) silica gel, cyclohexane-ethyl acetate gradients, (b) LiChroprep RP 18, MeOH-H_2O gradients, (c) Fractogel PVA 500, methanol. The separation scheme followed is set out in Figure 3, and the experimental conditions employed in each of the separation steps are set out in Table 2 below.

Purification and final separation was achieved by HPLC on silica gel Nucleosil 50 using cyclohexane-ethyl acetate (8:2) and high pressure liquid chromatography on silica gel RP 18 (LiChrosorb) using methanol-water mixtures, respectively. These procedures afforded the individual compounds **1** to **32** and **34** to **41** besides the mixtures **33**, **42** and **43**, whose identification was achieved by methylation or methanolysis and subsequent gas chromatographic analysis.

Table 2

Step No.	Applied to Fraction	Adsorbent	Eluent	Column dimensions	Fractions obtained
1	A.t.1 361 mg	Silica gel 40 g	Gradient CH/EA 10/0 0/10	D 1.2 cm L 46 cm	1 246 mg = 43 2 63 mg o 3 39 mg o
2	A.t.2 431 mg	Silica gel 40 g	Gradient CH/EA 10/0 0/10	D 1.2 cm L 46 cm	1 180 mg = 33 2 232 mg o 3 15 mg o
3	A.t.3 904 mg	Silica gel 160 g	Gradient	D 2.5 cm L 46 cm	1 209 mg o 2 611 mg = A.t. 3.2
4	A.t.3.2 611 mg	Silica gel 160 g	CH/EA 7/3	D 2.5 cm L 46 cm	1 150 mg o 2 431 mg = A.t. 3.2.2
5	A.t. 3.2.2 60 mg	Nucleosil RP-18, 7µm	M/EtOH 9/1	D 2 cm L 25 cm	1 55 mg = 32 2 4 mg o
6	A.t.4 1079 mg	Silica gel 640 mg	Gradient CH/EA 10/0 0/10	D 5 cm L 46 cm	1 39 mg o 2 10 mg o 3 156 mg = A.t. 4.3 4 308 mg = A.t. 4.4 5 322 mg = A.t. 4.5 6 51 mg = A.t. 4.6
7	A.T. 43 156 mg	Nucleosil RP-18, 7µm	M/W 96/4	D 2 cm L 25 cm	1 45 mg o 2 63 mg o 3 28 mg = 38
8	A.t. 4.4 308 mg	LiChroprep RP-18, 40 g	Gradient M/W 8/2 10/0	D 1.2 cm L 46 cm	1 235 mg = A.t. 4.4.1 2 31 mg o 3 9 mg o 4 17 mg o
9	A.t. 4.4.1 120 mg	Nucleosil RP-18, 7µm	M/W 84/16	D 2 cm L 25 cm	1 90 mg o 2 28 mg = 40
10	A.t. 4.5 30 mg	Silica Gel Si 60, 10µm	H/iso-PrOH 98/2	D 2 cm L 25 cm	1 15 mg o 2 11 mg = 39
11	A.t. 4.6 51 mg	LiChroprep RP-18, 40g	M/W 8/2	D 1.2 cm L 46 cm	1 23 mg = A.t. 4.6.1 2 20 mg o
12	A.t. 4.6.1 23 mg	Nucleosil RP-18, 7µm	M/W 9/1	D 2 cm L 25 cm	1 9 mg = 37 2 5 mg o
13	A.t. 4.6.2 20 mg	Nucleosil RP-18, 7µm	M/W 98/2	D 2 cm L 25 cm	1 1 mg o 2 1 mg o 3 13 mg = 36 4 4 mg = 35

Step No.	Applied to Fraction	Adsorbent	Eluent	Column dimensions	Fractions obtained
14	A.T. 5 784 mg	Silica gel 160 g	Gradient CH/EA 8/2 0/10	D 2.5 cm L 46 cm	1 115 mg = A.t. 5.1 2 121 mg ○ 3 60 mg = A.t. 5.3 4 201 mg = A.t. 5.4 5 145 mg ○ 6 54 mg = A.t. 5.6
15	A.t. 5.1 115 mg	PVA-500 30 g	MeOH	D 1 cm L 100 cm	1 72 mg ○ 2 8 mg ○ 3 38 mg = A.t. 5.1.3
16	A.t. 5.1.3 38 mg	PVA-500 15 g	MeOH	D 1 cm L 46 cm	1 5 mg ○ 2 30 mg = A.t. 5.1.3.2
17	A.t. 5.1.3.2 30 mg	Nucleosil RP-18, 7μm	M/W 95/5	D 0.8 cm L 25 cm	1 21 mg ○ 2 4 mg = 28
18	A.t. 5.3 60 mg	PVA-500 15 g	MeOH	D 1 cm L 46 cm	1 20 mg = A.t. 5.3.1 2 35 mg ○
19	A.t. 5.3.1 20 mg	PVA-500 15 g	MeOH	D 1 cm L 46 cm	1 17 mg = 21 2 1 mg ○
20	A.t. 5.4 201 mg	PVA-500 100 g	MeOH	D 2.5 cm L 100 cm	1 53 mg = 42 2 120 mg ○
21	A.t. 5.6 54 mg	LiChroprep RP-18, 40 g	M/W 1/1	D 1.2 cm L 46 cm	1 18 mg = 34 2 31 mg ○
22	A.t. 6 1750 mg	Silica gel 160 g	Gradient CH/EA 8/2 5/5	D 2.5 cm L 46 cm	1 3 mg ○ 2 1549 mg = A.t. 6.2 3 79 mg = A.t. 6.3 4 115 mg = A.t. 6.4
23	A.t. 6.2 1549 mg	LiChroprep RP-18, 160 g	M/W 7/3	D 2.5 cm L 46 cm	1 3 mg = A.t. 6.2.1 2 1540 mg = 16
24	A.t. 6.2.1 3 mg	Nucleosil RP-18, 7μm	M/W 75/25	D 2 cm L 25 cm	1 <1 mg ○ 2 2 mg = 6
25	A.t. 6.3 79 mg	Silica gel 9 g	$CHCl_3$	D 1 cm L 20 cm	1 30 mg = A.t. 6.3.1 2 29 mg = A.t. 6.3.2 3 11 mg = A.t. 6.3.3
26	A.t. 6.3.1 30 mg	LiChroprep RP-18, 40 g	M/W 6/4	D 1.2 cm L 46 cm	1 4 mg = 20 2 21 mg ○
21	A.t. 6.3.2 29 mg	LiChroprep RP-18, 40 g	M/W 55/45	D 1.2 cm L 46 cm	1 27 mg = 31 2 2 mg = 30
28	A.t. 6.3.3 11 mg	PVA 500 15 g	MeOH	D 1 cm L 40 cm	1 <1 mg ○ 2 10 mg = 29
29	A.t. 6.4 115 mg	Silica gel 40 g	$CHCl_3$	D 1.2 cm L 46 cm	1 11 mg ○ 2 16 mg = A.t. 6.4.2 3 73 mg = A.t. 6.4.3 4 5 mg = A.t. 6.4.4

Step No.	Applied to Fraction	Adsorbent	Eluent	Column dimensions	Fractions obtained
30	A.t. 6.4.2 16 mg	Nucleosil 40 g	M/W 6/4	D 2 cm L 25 cm	1 7 mg = 19 2 6 mg ○
31	A.t. 7 6177 mg	Silica gel 640 g	CH/EA 6/4 3/7	D 5 cm L 46 cm	1 1290 mg = 17 2 4350 mg = 7 3 40 mg = A.t. 7.3 4 91 mg = A.t. 7.4 5 52 mg = A.t. 7.5 6 11 mg = A.t. 7.6 7 328 mg = A.t. 7.7
32	A.t. 7.3 40 mg	LiChroprep RP-18, 40 g	M/W 5/5 9/1	D 1.2 cm L 46 cm	1 24 mg = A.t. 7.3.1 2 7 mg ○
33	A.t. 7.3.1 24 mg	LiChroprep RP-18, 40 g	M/W 3/7	D 1.2 cm L 46 cm	1 13 mg ○ 2 10 mg = A.t. 7.3.1.2
34	A.t. 7.3.1.2 10 mg	Nucleosil RP-18, 7μm	M/W 75.25	D 2 cm L 25 cm	1 2 mg ○ 2 3 mg ○ 3 2 mg = 12
35	A.t. 7.4 91 mg	LiChroprep RP-18, 40 g	Gradient M/W 5/5 9/1	D 1.2 cm L 46 cm	1 42 mg = A.T. 7.4.1 2 5 mg ○ 3 17 mg = A.t. 7.4.3 4 4 mg = 26
36	A.t. 7.4.1 42 mg	Nucleosil RP-18, 7μm	M/W 7/3	D 2 cm L 25 cm	1 3 mg ○ 2 7 mg = 9 3 13 mg = 10 4 <1 mg ○ 5 2 mg = 18
37	A.t. 7.4.3 13 mg	TSK HW 50s ca. 100 ml	MeOH	D 1 cm L 100 cm	1 11 mg = A.t. 7.4.3.1 2 1 mg ○
38	A.t. 7.4.3.1 11 mg (acetylated)	LiChrosorb Si 60, 10μm	CH/EA 8/2	D 2 cm L 25 cm	1 6 mg = 22 2 3 mg = 23
39	A.t. 7.5 52 mg	LiChroprep RP-18, 40 g	Gradient M/W 5/5 9/1	D 1.2 cm L 46 cm	1 30 mg = 4 2 9 mg ○
40	A.t. 7.6 11 mg	LiChroprep RP-18, 40 g	M/W 5/5	D 1.2 cm L 46 cm	1 4 mg = 13 2 6 mg ○
41	A.t. 7.7 328 mg	LiChroprep RP-18, 40 mg	Gradient M/W 1/1 10/0	D 1.2 cm L 46 cm	1 4 mg = 15 2 189 mg ○ 3 103 mg ○

Step No.	Applied to Fraction	Adsorbent	Eluent	Column dimensions	Fractions obtained
42	A.t. 8 771 mg	Silica gel 40 g	Gradient CH/EA 8/2 5/5 0/10	D 1.2 cm L 46 cm	1 384 mg = 8 2 165 mg = A.t. 8.2 3 44 mg = A.t. 8.3 4 93 mg = A.t. 8.4 5 34 mg = A.t. 8.5 6 8 mg = A.t. 8.6
43	A.t. 8.2 165 mg	LiChroprep RP-18, 40 g	M/W 75/25	D 1.2 cm L 46 cm	1 80 mg = A.t. 8.2.1 2 74 mg o
44	A.t. 8.2.1 80 mg	Silica gel 40 g	C/M 99/1	D 1.2 cm L 46 cm	1 15 mg = A.T. 8.2.1.1 2 20 mg = A.t. 8.2.1.2 3 36 mg o
45	A.t. 8.2.1.1 15 mg	PVA 500 15 g	M/C 9/1	D 1 cm L 45 cm	1 9 mg = 14 2 4 mg o
46	A.t. 8.2.1.2 20 mg	Preparative Silica gel- DC	C/M 99.5/0.5	Laufstrecke 10 cm	1 8 mg = 11 2 11 mg o
47	A.t. 8.3 44 mg	Nucleosil RP-18, 7µm	M/W 83/17	D 2 cm L 25 cm	1 7 mg = A.t. 8.3.1 2 8 mg = 5 3 19 mg o
48	A.t. 8.5 34 mg	Nucleosil RP-18, 7µm	M/W 9/1	D 2 cm L 25 cm	1 26 mg = 3 2 3 mg = 24
49	A.t. 8.6 8 mg	PVA 500 15g	MeOH	D 1 cm L 45 cm	1 3 mg - 2 2 4 mg o
50	A.t. 9 229 mg	Silica gel 80 g	Gradient CH/EA 8/2 5/5 0/10	D 2.5 cm L 23 cm	1 56 mg = A.t. 9.1 2 20 mg - A.t. 92. 3 136 mg o
51	A.t. 9.1 56 mg	Nucleosil RP-18, 7µm	M/W 96.4	D 2 cm L 25 cm	1 9 mg = 25 2 33 mg o
52	A.t. 9.2 20 mg	Nucleosil RP-18, 7µm	M/W 9/1	D 2 cm L 25 cm	1 4 mg = 1 2 13 mg o
53	A.t. 10 266 mg	Silica gel 40 g	C/M 10/0 95/5	D 1.2 cm L 46 cm	1 23 mg = A.t. 10.1 2 141 mg o 3 83 mg o
54	A.t. 10.1 23 mg	Silica gel 9 g	T/EA 6/4	D 1 cm L 18 cm	1 18 mg o 2 4 mg = 27

Abbreviations:

D: diameter, L: length, C: chloroform, CH: cyclohexane, EA: ethyl acetate, H: hexane, M: methanol, T: toluene, W: water

The compounds isolated from the benzene extract are listed below in Table 3. Those compounds already known as natural products are referred to in Table 3 by their chemical names, whilst those compounds not previously recognised as natural products are identified by code number. The full chemical names and spectroscopic and other characterising data for the new natural products are given in the paragraphs following Table 3.

Table 3

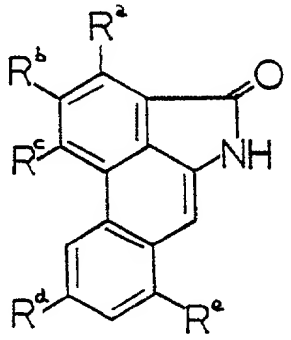
Compounds isolated from the Benzene Extract of the Root of *Aristolochia taliscana*

Compound Type	**Compound (Compound No.)**	**Content (%)***
Alkaloid	Aristolactam I (1)*	0.03
	Aristolactam A III (2)	0.02
	Aristolactam B III (3)	0.2
	Aristolactam C III (4)	0.2
	Taliscanine (5)	0.06
Lignans	Machilin-F (6)	0.02
Neolignans		
Benzofuran-type	Eupomatenoid-7 (7)	34
	Eupomatenoid-1 (8)	3
	Compound 9	0.05
	Compound 10	0.1
	Compound 11	0.06
	Compound 12	0.02
	Compound 13	0.03
	Compound 14	0.07
	Compound 15	0.03
Dihydro-benzofuran type	( )-Licarin A (16)	12
	(-)(2S,3S)-Eupomatenoid-8 (17)	10
	(-)(2S,3S)-Machilin-B (18)	0.02
	Compound 19	0.05
	(-)(2S,3S)-5-Methoxylicarin-A (20)	0.03

Compound Type	Compound (Compound No.)	Content (%)*
	(+)(2R,3R)-Dihydrocarinatidine (21)	0.1
Oligomers	Compound 22	0.05
	Compound 23	0.02
	Compound 24	0.02
	Compound 25	0.07
	Compound 26	0.03
Hybrids	Compound 27	0.03
	Compound 28	0.03
Phenylpropanes	Coniferyl alcohol (29)	0.08
	Ferulaaldehyde (30)	0.02
	Vanillin (31)	0.2
Sterols	Beta-sitosterol (32)	0.4
	Mixture of 3-O-acyl-beta-sitosterols (33)	1.4
Terpenoids	Compound 34	0.1
	Sandaracopimaradiene (35)	0.03
	Beta-caryophyllene (36)	0.1
	Caryophyllene oxide (37)	0.07
	ent-Germacrene-D (38)	0.2
	ent-Germacra-4(15), 5, 10 (14)-trien-1-beta-ol (39	0.09
	Spathulenol (40)	0.2
Others	D-fructose (41)	1.3
	Mixture of fatty acids (42)	0.4
	Mixture of triglycerides (43)	1.9

No aristolochic acids were detected in the extract.

The aristolactams referred to in the table have the following structural formulae:



	R^a	R^b	R^c	R^d	R^e
Aristolactam I	H	O-CH_2-O		H	OCH_3
Aristolactam A III	H	OH	OCH_3	OCH_3	H
Aristolactam B III	H	OCH_3	OCH_3	OCH_3	H
Aristolactam C III	CH_2OH	OCH_3	OCH_3	OCH_3	H
Taliscanine	H	OCH_3	OCH_3	OCH_3	H

Physico-chemical and Spectroscopic Properties of the Novel Natural Products

(±)-5-(1-Hydroxyallyl)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran (Compound 9).

Crystals (5 mg). Mp 164-167° (from MeOH). TLC: R_f 0.42(S-1); anisaldehyde: violet. $[\alpha]_D \pm 0°$ (c.0.1). IRν_{max} cm^{-1} :3540(OH), 3020, 1515. UVλ_{max} nm(logϵ):221(3.42), 305(3.38); +NaOH:212(3.82), 328(3,46). ^{1}H NMR(250 MHz): δ 2.00(1H,d,J = 3.5Hz,OH-8), 2.41(3H,s,Me-3),3.99(3H,s,OMe),4.03(3H,s,OMe),5.23(1H,dt,J_1 = 10.5,J_2 = 1.5Hz,H-10_B),5.31(1H,m,H-8),5.41(1H,dt,J_1 = 17,J_2 = 1.5Hz,H-10_A),5.75(1H,s,OH-14),6.14(1H,ddd,J_1 = 17,J_2 = 10.5,J_3 = 6Hz,H-9),6.83(1H,d,J = 1.5Hz,H-6),7.00(1H,d,J = 8Hz,H-15),7.12(1H,d,J = 1.5Hz, H-4, 7.29 (1H,dd,J_1 = 8,J_2 = 2Hz,H-16), 7.33(1H,d,J = 2Hz,H-12).

^{13}C NMR (60MHz):δ9.6(Me-3),56.5(2xOMe),76.5(C-8),106.6 (C-6),110.0(C-

12),110.9(C-3),111.3(C-4),114.6(C-15),116.5(C-10),121.2(C-16),124.5(C11),134.1(C3a),140.1(C-5),142.6(C-9),143.3(C-7a),146.2(C-7),148.1(C-14),149.2(C-13),152.9(C-2). EIMS m/z (rel. int.): 340[M]$^+$(100),323(14),297(11),295(11),284(12).

2-(4-Hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-5-(E)-propenylbenzofuran (Compound 10)

Crystals (12mg). Mp 175-179° (from MeOH). TLC:R_f0.3(S-1); anisaldehyde:grey. IRν_{max} cm^{-1}:3539(OH), 1600, 1515, 1466. UVλ_{max} nm(logϵ):231 (3.38), 266 (3.44),304 (3.34); +NaOH:240 (3.41), 295(3.25), 328(3.3). ^{1}H NMR (250 MHz): δ1.57(1H,t,J=4Hz, OH-3), 1.90(3H,dd,J_1=6.5J_2=1.5Hz, Me-10), 3.95(3H,s,OMe),4.04(3H,s,OMe),4.91(2H,d,J=4Hz,CH_2OH),5.81(1H,s,OH-14), 6.23(1H,dq,J_1=16,J_2=6.5Hz,H-9), 6.48(1H,dq,J_1=16,$J_2$1.5Hz,H-8), 6.83(1H,d,J=1.5Hz,H-6), 7.01(1H,d,J=8Hz,H-15), 7.18(1H,d,J=1.5Hz,H-4), 7.38(1H,dd,J_1=8,J_2=2Hz,H-16), 7.41(1H,d,J=2Hz,H-12). ^{13}C NMR:δ18.4(Me-10), 55.7(CH_2OH), 56.1(2xOMe), 104.8(C-6), 109.0(C-4), 110.0(C-12), 113.8(C-3), 114.7(C-15), 121.3(C-16), 122.4(C-11), 124.8(C-9), 131.2(C-3a), 131.3(C-8), 123.3(C-5), 142.3(C-7a), 145.0(C-7), 146.6(C-14), 146.7(C-13), 154.6(C-2). EIMS m/z(rel.int):340[M]$^+$(100), 323(15),291(19),151(10).

2-(4-Hydroxy-3-methoxyphenyl)-7-methoxy-3-methyl-5-[(E)-3-oxopropenyl]benzofuran (Compound 11)

Crystals (8 mg). Mp 169-170° (from MeOH). TLC:R_f0.39(S-1); anisaldehyde:blue. IR ν_{max} cm^{-1}:3538(OH), 1672(CO), 1610, 1514. UV λ_{max} nm(logϵ):213(4.04), 291(4.91), 314(4.31); +NaOH:215(4.93), 337(4.36). ^{1}H NMR(250MHz):δ2.46(3H,s,Me-3), 3.99(3H,s,OMe), 4.08(3H,s,OMe), 6.73(1H,dd,J_1=16,J_2=8Hz,H-8), 7.00(1H,d,J=2Hz,H-6), 7.04(1H,d,J=2Hz,H-15), 7.30(1H,d,J=8Hz,H-16), 7.32(1H,dd,J_1=8,J_2=2Hz,H-12), 7.33(1H,d,J=2Hz,H-4), 7.58(1H,d,J=16Hz,H-8), 9.72(1H,d,J=8Hz,CHO). ^{13}CNMR(60MHz):δ9.5(Me-3), 56.1(2xOMe), 105.7(C-6), 109.6(C-12), 110.1(C-3), 113.8(C-4), 114.7(C-15), 120.8(C-16), 122.9(C-11), 124.5(C-9), 129.7(C-5), 133.5(C-3a), 144.7(C-7a), 145.4(C-7), 146.3(C-14), 146.8(C-13), 152.6(C-2), 153.9(C-8), 193.6(C-10). EIMS m/z (rel. int.):338[M]$^+$(96), 311(19), 310(100), 295(28), 267(29), 178(10), 169(12), 165(12), 152(11).

5-Formyl-3-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran (Compound 12)

Crystals (2 mg). Mp 162-165° (from MeOH). TLC:R_f0.43(S-1); anisaldehyde:light blue. IRν_{max} cm^{-1}:3540(OH), 3023, 1688(CO), 1515. UV λ_{max} nm(logϵ):231(4.40), 283(4.61), 307(sh,4.53); +NaOH:240(4.44), 329(4.62). ^{1}HNMR:δ2.48(3H,s,Me-3), 4.00(3H,s,OMe), 4.07(3H,s,OMe), 5.80(1H,s,OH), 7.03(1H,d,J=8Hz,H-15), 7.32(1H,dd,J_1=8, J_2=2Hz,H-16), 7.33(1H,d,J=2Hz,H-12), 7.37(1H,d,J=1.5Hz,H-4), 7.68(1H,d,J=1.5Hz,H-6), 10.0(1H,s,CHO). ^{13}C NMR: δ9.5(Me-3), 56.1(2xOMe), 104.7(C-6), 110.5(C-3), 114.6(C-4), 117.4(C-15), 120.8(C-16), 122.8(C-11), 132.9(C-3a), 133.1(C-5), 145.8(C-7), 146.2(C-14), 146.4(C-13), 146.8(C-7a), 153.0(C-2), 192.0(CO). EIMS m/z (rel. int.):312[M]$^+$(100), 297(14), 269(12), 156(15).

2-(4-Hydroxy-3-methoxyphenyl)-5-[(E)-3-hydroxypropenyl]-7-methoxy-3-methylbenzofuran (Compound 13)

Crystals (7 mg). Mp 180-183° (from MeOH).

TLC:R_f0.16(S-1); anisaldehyde:violet. IRν_{max} cm^{-1}:3540(OH), 3020, 1612, 1515. UV λ_{max} nm(logϵ):232(3.16), 271(3.30), 306(sh 3.23); +NaOH:240(3.29), 291(3,19), 329(3.33). ^{1}H NMR δ1.45(1H,t,J=5.5Hz, OH-10), 2.41(3H,s,Me-3), 3.99(3H,s,OMe), 4.05(3H,s,OMe), 4.35(2H,dd,J_1=5.5,J_2=1Hz,CH_2OH), 5.75(1H,s,OH-14), 6.37(1H dt,J_1=16,J_2=5.5Hz,H-9), 6.71(1H,dt,J_1=16,J_2=1Hz,H-8), 6.88(1H,d,J=1.5Hz,H-6), 7.00(1H,d,J=8.5Hz,H-15), 7.11(1H,d,J=1.5Hz,H-4), 7.29(1H,dd,J_1=8.5,J_2=2Hz,H-16), 7.32(1H,d,J=2Hz,H-12). ^{13}C NMR:δ9.6(Me-3), 56.1(2xOMe), 63.8(C-10), 104.8(C-6), 109.5(C-4), 110.2(C-3 and C-12), 114.4(C-15), 120.7(C-16), 123.5(C-11), 127.2(C-9), 132.1(C-8), 132.3(C-3a), 133.2(C-5), 142.6(C-7a), 145.0(C-7), 145.8(C-14), 146.6(C-13), 151.8(C-2). EIMS m/z (rel. int.): 340[M]$^+$(100), 312(12), 311(20), 297(22), 284(37), 282(15), 281(12), 279(11), 165(13), 151(14), 149(10), 55(10).

2-(3,4-Dihydroxyphenyl)-7-methoxy-3-methyl-5-(E)-propenylbenzofuran (Compound 14)

Oil (9 mg). TLC:R_f0.15(S-2); anisaldehyde:grey. IR ν_{max} cm^{-1}:3548(OH), 3015, 1600, 1523, 1483. UV λ_{max} nm(logϵ):231(4.49), 264(4.59), 207(sh.4.46);

+NaOH:242(4.60), 327(4.44). ^{1}H NMR(CD_3OD, 250 MHz):δ1.88(3H,dd,J_1=6.5,J_2=1.5Hz,Me-10),2.37(3H,s,Me-3),4.01(3H,s,OMe), 6.22(1H,dq,J_1=16,J_2=6.5Hz,H-9), 6.47(1H,dq,J_1=16,J_2=1.5Hz,H-8), 6.85(1H,d,J=1.5Hz,H-6), 6.88(1H,d,J=8.5Hz,H-15), 7.01(1H,d,J=1.5Hz,H-4), 7.14(1H,dd,J_1=8.5Hz,J_1=2Hz,H-16), 7.26(1H,d,J=2Hz,H-12). ^{13}C NMR(CD_3OD,60MHz):δ9.6(Me-3),18.6(Me-10), 56.7(OMe), 105.8(C-6), 110.1(C-4), 110.5(C-3), 114.9(C-12), 116.6(C-15), 119.9(C-16), 124.5(C-11), 124.8(C-9), 132.9(C-8), 134.4(C-3a), 135.1(C-5), 143.3(C-71), 146.2(C-7), 146.5(C-14), 146.9(C-13), 152.9(C-2). EIMS m/z (rel. int.):310[M]$^+$(100), 309(10).

<u>*erythro*-5-(1,2-Dihydroxypropyl)- 2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran (Compound 15)</u>

Amorphous (3 mg). TLC:R_f0.16(S-2);anisaldehyde:violet. $[\alpha]_D$+17°(c0.2). IR ν_{max} cm^{-1}:3435(OH), 2927, 1655, 1516, 1462. UV λ_{max} nm(logϵ):216(4.16), 304(4.04): +NaOH:211 (4.80), 328(4.11). ^{1}HNMR:δ1.11(3H,d,J=6.5Hz,Me-10), 2.42(3H,s,Me-3), 2.44(1H,br d,J=3Hz, O<u>H</u>-9), 2.61(1H,br d,J=3HZ,O<u>H</u>-8), 3.90(1H,m,H-9), 3.99(3H,s,OMe), 4.05(3H,s,OMe), 4.48(1H,dd,J_1=7.5,J_2=3Hz,H-8), 5,75(1H,s,O<u>H</u>-14), 6.80(1H,d,J=1.5Hz,H-6), 7.01(1H,d,J=8Hz,H-15), 7.10(1H,d,J=1.5Hz,H-4),7.30(1H,dd,J_1=8,J_2=2Hz,H-16),7.33(1H,d,J=2Hz,H-12). ^{13}C NMR(60MHz):δ9.6(Me-3), 16.9(Me-10), 56.1, 56.2(2xOCH_3), 72.5(C-9), 80.1(C-8), 105.3(C-6), 109.5(C-12), 109.9(C-4), 110.1(C-3), 114.5(C-15), 120.7(C-16), 123.5(C-11), 133.0(C-3a), 136.4(C-5), 142.5(C-7a), 145.0(C-7), 145.9(C-14), 146.6(C-13), 152.6(C-2). EIMS m/z (rel.int.):358[M]$^+$(100), 328(16), 314(21), 313(81), 285(52), 258(11), 257(57), 253(28), 225(14), 133(13).

<u>(2R,3R)-2,3-Dihydro-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-5-(E)-propenylbenzofuran (Compound 19)</u> Amorphous (6 mg). TLC:R_f0.3(S-1); anisaldehyde:red. $[\alpha]_D$+65°(c.0.2). CDλ_{max} nm$\Delta\epsilon$):235(-3.15), 260(+3.14), 285(+2.39). IRν_{max} cm^{-1}:3543(OH),3019,1613,1518,1499,1466. UVλ_{max} nm(logϵ):204(4.59),218(4.49),273(4.23);+NaOH:211(4.93), 268(4.38). ^{1}H NMR(CD_3OD):δ1.78(3H,dd,J_1=6,J_2=2Hz,Me10), 3.47(1H,m,H-3), 3,78(2H,d,J=7Hz,C<u>H_2</u>OH), 3.80(3H,s,OMe), 3.86(3H,s,OMe), 5.50(1H,d,J-6Hz,H-2), 6.11(1H,dq,J_1=16,J_2=6.5Hz,H-9), 6.33(1H,dq,J_1=16,J_2=2Hz,H-8), 6.76(1H,d,J=8Hz,H-15), 6.82(1H,dd,J_1=8,J_2=2Hz,H-16), 6.86(1H,br s,H-4),

6.88(1H,br s,H-6), 6.94(1H,d,J=2Hz,H-12). ^{13}C NMR(60MHz):18.3(Me-10), 53.7(C-3), 56.0(2xOMe), 64.0(CH_2OH-3), 88.7(C-2), 108.8(C-12), 110.0(C-6), 113.9(C-4), 114.3(C-15), 119.4(C-16), 123.8(C-9), 127.9(C-11), 129.7(C-8), 132.3(C-5), 133.0(C-3a), 144.4(C-7), 145.7(C-14), 146.7(C-7a), 147.6(C-13), EIMS m/z (rel.int.):342$[M]_+$(52), 324(78), 310(20), 309(100), 293(28), 292(32), 221(10), 165(14), 152(13), 151(22), 137(17).

erythro-1-(4-Acetoxy-3-methoxyphenyl)-2-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propylacetate (Compound 22)

Colourless crystals (5 mg). MP 156-158° (from MeOH). TLC:R_f0.54(S-3); anisaldehyde:grey. $[\alpha]_D$+18°(c.0.1). IRν_{max} cm^{-1}:3018, 1762,1741,1510. UV λ_{max} nm(logϵ):226(4.08), 266(4.10), 308(4.08). ^{1}H NMR:δ1.31(3H,d,J=6.5Hz, Me-9′), 1.89(3H,dd,J_1=6.5,J_2=1.5Hz,Me-10), 2.11(3H,s,MeCO-7′), 2.25(3H,s,MeCO-4′), 2.40(3H,s,Me-3), 3.83(3H,s,OMe), 3.89(3H,s,OMe), 4.01(3H,s,OMe), 4.77(1H,m,H-8′), 5.91(1H,d,J=4.5Hz,H-7′), 6.24(1H,dq,J_1=16,J_2=6Hz,H-9), 6.50(1H,dq,J_1=16,J_2=1.5Hz,H-8), 6.80(1H,d,J=1.5Hz,H-6), 6.91(1H,d,J=8Hz,H-15), 6.96(1H,d,J=8.5Hz,H-6′), 6.97(1H,dd,J_1=8.5, J_2=2HzH-5′), 7.01(1H,br s,H-4), 7.08(1H,d,J=2Hz,H-2′), 7.29(1H,dd,J_1=8,J_2=2Hz,H-16), 7.32(1H,d,J=2Hz,H-12). ^{13}C NMR:δ9.6(Me-3), 15.5(Me-9′), 18.4(Me-10), 20.7(MeCO-4′), 21.2(MeCO-7′), 56.0,56.1(3xOMe), 76.6(C-7′),78.0(C-8′),104.7(C-6),109.2(C-4),110.8(C-3),111.3(C-12),112.1(C-2′),117.7(C-5′),119.6(C-15),119.9(C-6′),122.4(C-16),124.4(C-9),125.8(C-11), 131.5(C-8), 133.0(C-3a), 133.7(C-5), 135.9(C-1′), 139.6(C-14′), 142.2(C-7a), 144.9(C-7), 147.1(C-14), 150.9(C-13), 151.3(C-3′), 168.9(MeCO-4′), 169.9(MeCO-7′). EIMS m/z (rel.int.):588$[M]_+$(6), 366(14), 325(20), 324(100), 265(31), 223(54), 181(27), 164(25).

threo-1-(4-Acetoxy-3-methoxyphenyl)-2-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propyl-acetate (Compound 23)

Mp 155-158° (from MeOH). TLC:R_f0.54(S-3); anisaldehyde:grey. $[\alpha]_D$+35°(c.0.1). IRν_{max} cm^{-1}:3018,1762,1741,1510. UV λ_{max} nm(logϵ):226(4.08), 266(4.10), 308(4.08). ^{1}HNMR: δ1.24(3H,d,J=6.5Hz,Me-9′). 191(3H,dd,J_1=6.5, J_2=2Hz,Me-10), 2.04(3H,s,MeCO-7′), 2.30(3H,s,MeCO-4′), 2.43(3H,s,Me-3), 3.85(3H,s,OMe), 3.92(3H,s,OMe), 4.04(3H,s,OMe),

4.65(1H,m,H-8'), 5.99(1H,d,J=6.5Hz,H-7'), 6.22(1H,dq,J_1=16,J_2=6.5Hz, H-9), 6.50(1H,dq, J_1=16,J_2=2Hz,H-8),6.84(1H,d,J=1.5Hz,H-6), 6.99(1H,dd,J_1=8,J_2=2Hz, H-16), 7.02(1H,d,J=8Hz,H-15), 7.03(1H,d,J=1.5Hz,H-4), 7.03(1H,d,J= 8.5Hz H-15'), 7.04(1H,d,J=2Hz,H-12), 7.31(1H,dd,J_1=8.5,J_2=2Hz,H-16'), 7.35(1H,d,J=2Hz,H-12'), ^{13}CNMR:δ9.6(Me-3), 16.7(Me-9'), 20.7(MeCO-4'), 21.1(MeCO-7'), 56.0,56.1(3xOMe), 76.6(C-7'), 77.8(C-8'), 104.6(C-6), 109.2(C-4), 110.7(C-3), 111.2(C-12), 111.9(C-2'), 116.8(C-5'), 119.8(C-15), 119.9(C-6'), 122.7(C-16), 124.4(C-9), 125.5(C-11), 131.5(C-8), 133.0(C-3a), 133.7(C-5), 136.0(C-1'), 139.8(C-4'), 142.2(C-7a), 144.9(C-7), 147.8(C-14), 150.5(C-2), 151.0(C-13), 151.2(C-3'), 168.8(MeCO-4'), 169.9(MeCO-7'). EIMS m/z (rel.int.):588[M]$_+$(6), 366(15), 325(20), 324(100), 265(30), 223(54), 181(27), 164(25).

threo-1-[2-(4-Hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran-5-yl]-2-[4-(3-methyl-5-(e)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propan-1-ol (Compound 24)

Amorphous (3mg). TLC:R_f0.69(S-2); anisaldehyde:violet. $[\alpha]_D$+20°(c.0.2). IRν_{max} cm^{-1}:3540(OH),3020,2938,1614,1511,1466. UVλ_{max} nm(logϵ):229(4.16), 266(4.20), 308(4.14); +NaOH: 239(4.43), 330(4.46). ^{1}H NMR: δ0.98(3H,d,J=6.5Hz,Me-10'), 1.89(3H,dd,J_1=6.5, J_2=1.5Hz,Me-10), 2.36(3H,s,Me-3'), 2.43(3H,s,Me-3),3.98,4.01,4.02,4.06 (12H,s.4xMe), 4.22(1H,m,H-9'), 4.69(1H,d,J=8.5Hz,H-8'), 5.74(1H,s,OH-14'), 6.20(1H,dq,J_1=16,J_2=6.5Hz,H-9), 6.48(1H,dq,J_1=16,J_2=1.5Hz-H-8), 6.81(1H,d,J=8.5Hz,H-15), 6.81(1H,d,J=1.5Hz,H-6), 6.89(1H,d,J=1.5Hz,H-6'), 7.00(1H,d,J=8Hz,H-15'), 7.01(1H,d,J=1.5Hz,H-4), 7.07(1H,dd,J_1-8.5, J_2=2Hz,H-16), 7.09(1H,d,J=1.5Hz,H-4'), 7.29(1H,dd, J_1=8.5,J_2 = 2Hz,H-16'), 7.31(1H,d,J=2Hz,H-12'),7.35(1H,d,J=2Hz,H-12). ^{13}CNMR:δ9.6(Me-3), 9.7(Me-3'), 18.0(Me-10'), 18.4(Me-10), 56.0, 56.1,56.3(4xOMe), 71.8(c-9'), 91.3(C-8'), 104.7(C-6), 105.4(C-6'), 109.2(C-4), 109.6(C-12'), 110.2(C-12), 110.4(c-4'), 110.6(C-3), 110.9(C-3'), 114.5(C-15), 118.5(C-15'), 119.8(C-16), 120.8(C-16'), 123.2(C-11'), 124.5(C-9), 126.2(C-11), 131.4(C-8), 132.9(C-31'), 133.1(C-3a), 133.7(C-5), 133.9(C-5'), 142.2(C-7a), 142.6(C-7a'), 144.9(C-7), 145.2(C-7'), 145.9(C-14'), 146.6(C-13'), 147.9(C-4), 150.7(C-13), 151.1(C-2'), 151.9(C-2). DCIMS m/z (rel.int.):665[m+h]$^+$(10), 381(9), 367(12), 343(12), 342(25),

341(100), 340(24), 326(22), 325(94), 324(44).

2-Methoxy-4-[7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl]-6-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]phenol (Compound 25)

Amorphous (9 mg). TLC:R_f0.83(S-1); anisaldehyde:grey. IRν_{max} cm^{-1}:3538(OH), 3020, 2939, 1613, 1599, 1510. UV λ_{max} nm(logϵ):233(4.14),267(4.48),309(4.46); +NaOH:215(5.23), 316(4.41). ^{1}H NMR(250 MHz):δ1.91(6H,m,Me-10 and Me10'), 2.31(3H,s,Me-3'), 2.42(3H,s,Me-3),3.99,4.01,4.04(12H,s,4xOMe), 6.20(2H,m,H-9 and H-9'),6.47(1H,dq,J_1 = 16,J_2 = 1.5Hz,H-8'), 6.50(1H,dq,J_1 = 16,$_2$ = 1.5Hz,H-8),6.81(1H,d,J = 1.5Hz,H6'),6.84(1H,d, J = 1.5Hz,H-6),7.00(1H,d,J = 1.5Hz,H-4'),7.03(1H,d,J = 1.5Hz,H4),7.04 (1H,d,J = 2Hz,H-12'),7.05(1H,d,J = 8Hz,H-15),7.18(1H,d,J = 2Hz,H16'), 7.31(1H,dd,J_1 = 8,J_2 = 2Hz,H-16),7.45(1H,d,J = 2Hz,H12). ^{13}C NMR(60MHz): δ9.5,9.6(Me-3,Me-3'), 18.4(Me-10,Me-10'), 56.1,56.3,56.5(4xOMe), 104.7,104.8(C-6,C-6'), 106.1(C-16'), 109.3,109.8(C-4,C-4'), 111.2(C-3'), 111.3(C-12), 111.5(C-3), 111.9(C-12'), 116.8(C-15), 119.9(C-16), 122.8(C-11), 124.4,124.5(C-9,C-9'), 127.6(C-11'), 132.7,132.9(C-8,C-8'), 133.7,133.8(C-3a,C-3a'), 137.3(C-14'), 142,1,142.3(C-71,C-7a'), 143.8(C-14), 144.8,144.9(C-7,C-7'), 145.8(c-15'), 148.2(C-13,C-13'),150.4, 150.9(C-2,C-2'). DCIMS m/z (rel.int.):647[M+H]$^+$(100), 646(44), 473(18), 369(12), 341(26), 339(16), 326(11), 325(46), 324(23), 309(34), 308(13), 283(20), 113(19), 107(18), 105(12).

8.2',9.3'-Tetrahydro-bis-eupomatenoid-7 (Compound 26)

Crystals (4 mg). Mp 175-179° (from MeOH). TLC:R_f0.26(S-1); anisaldehyde:grey-blue. $[\alpha]_D$ ± 0°(c.0.1). IRν_{max} cm^{-1}:3540(OH), 3020,1618,1465. UV λ_{max} nm(logϵ) 217(5.03), 279(4.83), 297(sh 4.79), +NaOH: 261(4.76), 305(4.75), 327(sh 4.78). ^{1}H NMRδ1.05(3H,s,Me-3'), 1.31(3H,d,J = 6.5Hz,Me-10), 1.86(3H,dd,J_1 = 6.5,J_2 = 1.5Hz,Me-10'), 2.37(3H,s,Me-3),2.97(1H,dq, J_1 = 11,J_2 = 6.5Hz,H-9), 3.50(3H,z,OMe-13'), 3.76(1H,d,J = 11Hz,H-8), 3.80(3H,s,OMe-7), 3.92(3H,s,OMe-13'), 4.00(3H,s,OMe-7'), 6.17(1H,dq, J_1 = 16,J_2 = 6.5Hz,H-9'), 6.42(1H,dq,J_1 = 16,J_2 = 1.5Hz,H-8'), 6.48(1H,s,H-6), 6.63(1H,d,J = 8.5Hz,H-15'), 6.75(1H,d,J = 2Hz,H-12'), 6.83(1H,dd, J_1 = 8.5, J_2 = 2Hz,H-16'),6.85(1H,d,J = 1.5Hz,H-4'),6.90(1H,d,J = 8Hz,H-15),6.94(1H,s,H-

4), 6.98(1H,d,J=1.5Hz,H-6'), 7.22(1H,dd,J_1=8,J_2=2Hz,H-16), 7.33(1H,d,J=2Hz,H-12). ^{13}C NMR:δ9.6 (Me-3), 16.2(Me-10), 18.5(Me-10'), 22.1(Me-3'), 42.7(C-9), 56.2(C-3'), 56.5,56.7,57.3,58.2(4xOMe), 98.1(C-8), 107.9(C-2'), 109.7(C-6), 110.6(C-4), 110.9(C-6'), 111.3(C-12), 111.8(C-4'), 115.5(C-15'),116.5(C-15),117.4(C-12'),120.7(C-16'),121.2(C-16),124.1(C-9'), 124.5(C-11), 128.8(C-11'), 132.4(C-8'), 133.7(C-5'), 134.0(C-3a), 135.3(C-5), 136.0(C-3a'), 142.5(C-7a), 146.0(C-7), 146.4(C-7'), 146.9(C-13'), 147.7(C-7a'), 148.0(C-14'), 149.2(C-14), 152.6(C-2). CIMS m/z (rel.int.):649[M+H]$^+$ (13), 648(7), 367(12), 326(25), 325(100), 324(88).

15-(Aristolactam-I-9-yl)-eupomatenoid-7 (Compound 27)

Yellow crystals (4 mg). Mp 165-170° (from MeOH). TLC:R_f0.43(S-2); anisaldehyde:green. IRν_{max}cm^{-1}:3531,3442,3020,3011,1699,1610,1482,1466. UV λ_{max} nm(logϵ):256 (4.83), 267(sh 4.79), 301(4.73), 405(4.00). ^{1}H NMR (C_5D_5N):δ1.86 (3H,dd,J_1=6.5,J_2=1.5Hz,Me-10), 2.44(3H,s,Me-3), 3.52(3H,s,OMe-8'), 3.80(3H,s,OMe-13), 3.96(3H,s,OMe-7), 6.30(1H,dq,J_1=16,J_2=6.5Hz,H-9), 6.34(2H,d,J=1Hz,OC<u>H$_2$</u>O), 6.63(1H,dq,J_1=16,J_2=1.5Hz,H-8), 7.09(1H,d,J=1.5Hz,H-6), 7.13(1H,dd,J_1=8,J_2=1Hz,H-7'), 7.27(1H,d,J=1.5Hz,H-4),7.57(1H,d,J=2Hz,H-12), 7.58(1H,t,J=8Hz,H-6'), 7.81(1H,d,J=2Hz,H-16), 7.84(1H,s,H-2'), 8.57(1H,dd,J_1=8,J_2=1Hz,H-5'), 11.26(1H, br s,O<u>H</u>), 12.02(1H,br s, N<u>H</u>). ^{13}C NMR(C_5D_5N):δ9.8(Me-3), 18.5(C-10), 55.9,56.4,56.5(3xOCH$_3$), 103.4(OCH$_2$O), 105.1(c-6), 106.0(C-2'), 109.6,,109.7(C-4,C-12), 111.5(C-7'), 112.6(C-4a'), 113.2(C-9'), 121.0(C-1'), 121.8(C-5'), 122.4(C-16), 124.4(C-9), 125.6(C-4b'), 126.1(C-6'), 127.9(C-11), 129.0(C-15), 132.3)C-8), 133.8(C-3a), 134.3(C-5), 136.1(C-10'), 142.6(C-7a), 145.6(C-7), 146.6(C-14), 147.7(C-4'), 148.6(C-13), 149.0(C-3'), 152.2(C-2), 158.8(C-8'), 169.7(CO). EIMS m/z (rel.int.): 615[M]$^+$(100), 584(12), 583(11), 308(25), 292(14), 285(10).

14-O-α-Cadinyl-eupomatenoid-7 (Compound 28)

Oil (3.5 mg). TLC:R_f0.78(S-1); anisaldehyde:grey. [α]$_D$+39°(C.0.3). IRν_{max} cm^{-1}:3019,2917,1614,1599,1505,1481,1450. UV λ_{max} nm(logϵ): 235(4.45), 265(4.48), 311(4.39). ^{1}H NMR:δ0.77(3H,d,J=7Hz,Me-13' or Me-14'), 0.90(3H,d,J=7Hz,Me-13' or Me-14'), 1.25(3H,s,Me-15'), 1.71(3H,s,Me-11'),

1.92(3H,dd,J_1=6.5,J_2=1.5Hz,Me-10), 2.43(3H,s,Me-3), 3.90(3H,s,OMe-13), 4.04(3H,s,OMe-7), 5.53(1H,br s,H-4'), 6.22(1H,dq,J_1=16,J_2=6.5Hz,H-9), 6.51(1H,dq,J_1=16,J_2=1.5Hz,H-8),6.83(1H,d,J=2Hz,H-6),7.04(1H,d,J=8Hz,H-15), 7.05(1H,d,J=2Hz,H-4), 7.26(1H,dd,J_1=8,J_2=2Hz,H-12), 7.32(1H,d,J=2Hz,H-16). ^{13}C NMR:δ9.7(Me-3), 15.1(Me-13'), 18.4(Me-10), 18.5(Me-15'), 21.5(Me-14@), 21.9(C-9'), 23.1(C-1'), 23.9(Me-11'), 25.9(C-12'), 31.0(C-2'), 37.7(C-8'), 40.2(C-5'), 46.3(C-6'), 48.0(C-10'), 55.8,56.1(2xOMe), 84.9(C-9'), 104.7(C-6), 109.2(C-4), 110.9(C-12), 111.8(C-3), 119.2(C-16), 122.4(C-4'), 124.4(C-9), 125.8(C-15), 127.1(C-11), 131.5(C-8), 133.1(C-3a), 133.7(C-5), 135.2(C-3'), 142.3(C-7a), 144.9(C-14), 151.4(C-2), 154,5(C-13). DCIMS m/z (rel.int.):529[M+H]$^+$(41), 528(14), 367(16), 326(11), 325(51), 324(100), 206(15), 205(93), 203(6).

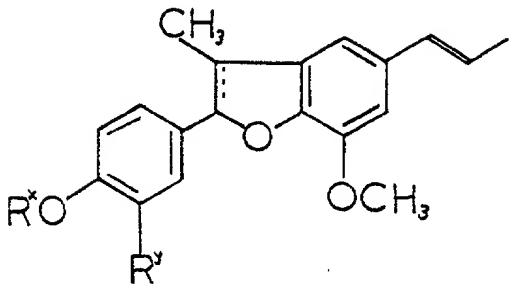
(2R,4S)-2-Hydroxy-6-methoxy-4,7-dimethyl-1-tetralone (Compound 34) Amorphous (17 mg). TLC:R_f0.44(S-1); anisaldehyde:yellow. $[\alpha]_D$-39°(c.01). CDλ_{max} nm($\Delta\epsilon$):220(+3.74), 270(-2.09), 295(+3.52), 315(-143). IRν_{max} cm^{-1}:3496(OH), 3016,1674,(CO),1609,1497. UV λ_{max} nm(logϵ):225(4.12), 274(4.09). ^{1}H NMR(250 MHz):δ1.46(3H,d,J=6.5Hz,Me-e), 176(1H,ddd,J_1=13.5, J_2=J_3=12.5Hz, H-3_{ax}), 2.21(3H,br s,Me-7), 2.48(1H,ddd,J_1=12.5, J_2=J_3=5.5Hz,H-3_{eq}), 3.16(1H,m,H-4), 3.91(3H,s,OMe), 4.33(1H,dd,J_1=13.5, J_2=5.5Hz,H-2_{ax}), 6.77(1H,br s,H-5), 7.84(1H,br d,J=1Hz,H-8).
^{13}C NMR(60MHz):δ15.7(Me-7), 20.5(Me-4), 31.6(C-4), 40.8(C-3), 55.5(OMe), 73.0(C-2), 107.0(C-5), 122.8(C-8a), 126.1(C-7), 129.7(C-8), 149.0(C-4a), 162.9(C-6), 198.5(CO). EIMS m/z (rel.int.):220[M]$^+$(68), 202(25), 177(19), 176(100), 175(61), 174(31), 159(12), 148(33), 147(14), 133(37), 117(14), 115(13).

EXAMPLE 2

DETERMINATION OF MUTAGENIC AND ANTIMUTAGENIC ACTIVITY

The four major constituents of the benzene extract from *Aristolochia taliscana* roots - eupomatenoid-7 (**7**), eupomatenoid-1 (**8**), eupomatenoid-8 (**17**), Licarin-A (**16**) - were tested for their mutagenic and antimutagenic properties using the Ames bio-assay (Maron, D.M. and Ames, B.N., Mutation Research, 1983, **113**,

173). The test compounds have the following structural formula:



Eupomatenoid-1: R^x & R^y = OCH_2O, dotted line = double bond

Eupomatenoid-7: R^x = OH, R^y = OCH_3, dotted line = double bond

Eupomatenoid-8: R^x & R^y = OCH_2O, dotted line = single bond

Licarin-A: R^x = OH, R^y = OCH_3, dotted line = single bond

Method

Salmonella typhimurium strain TA 100 was used as the test organism and 2-amino-anthracene (2-AA) and 2-nitrofluorene (2-NF) as standard mutagens, of which 1μg were added to each test plate. In the experiments with 2-AA, "S9 Mix" (derived from phenobarbital treated rat liver cells (De Flora, S., Camoirana, A., D'Agostini, F. and Balansky, R., Mutation Research, 1992, **267**, 183) was also added.

Results

None of the tested substances showed any mutagenic activity. Eupomatenoid-7 (**7**) exhibited strong antimutagenic effects against 2-aminoanthracene as well as against 2-nitrofluorene (Tab. 4). Licarin-A (**16**) and eupomatenoid-1 (**8**) were found to be antimutagenically active only in the experiment against 2-AA but not against 2-NF (Tab. 5). However, eupomatenoid-8 (**17**) did not show any antimutagenic effect in the test systems used (Tab. 6).

Eupomatenoid-7 (**7**)

Amount of compound added [μg]	Residual mutagenic activity (%) observed for:	
	2-AA	2-NF
50	4	16
100	0	0

Table 4: Results from the experiments on antimutagenic activity of eupomatenoid-7 (**7**).

(±)-Licarin-A (**6**)

Amount of compound added [μg]	Residual mutagenic activity (%) observed for	
	2-AA	2-NF
50	31	94
100	6	85

Table 5: Results from the experiments on antimutagenic activity of (±)-licarin-A (**6**)

Eupomatenoid-1 (8)

Amount of compound added [μg]	Residual mutagenic activity (%) observed for	
	2-AA	2-NF
50	49	99
100	44	93

Table 6: Results from the experiments on antimutagenic activity of eupomatenoid-1 (**8**)

Eupomatenoid-8 (17)

Amount of compound added [μg]	Residual mutagenic activity (%) observed for	
	2-AA	2-NF
50	90	100
100	73	95

Table 7: Results from the experiments on antimutagenic activity of eupomatenoid-8 (17).

EXAMPLE 4
CYTOTOXICITY STUDIES

The cytotoxicity of compounds isolated from *Aristolochia Taliscana* was assayed using the well known brine shrimp bioassay. The cytotoxicities of compounds of the invention, expressed as percentage "death rates" after 24 hours, at varying concentrations, are shown in Table 8 below.

Table 8: Cytotoxicities of Compounds in the Brine Shrimp Assay

SUBSTANCE	"Death Rate" After 24 Hours (%)			LC_{50}
	10ppm	100ppm	500ppm	(ppm)
Aristolactam B (**3**)	5	9	29	>500
Aristolactam C (**4**)	0	0	3	>500
Eupomatenoid-7 (**7**)	27	38	38	>500
Eupomatenoid-1 (**8**)	12	16	20	>500
Licarin-A (**16**)	93	93	96	<10
Eupomatenoid-8 (**17**)	9	27	42	>500
Dihydrocarinatidine (**21**)	26	53	80	ca. 120
Coniferyl alcohol (**29**)	0	0	15	>500
Vanillin (**31**)	5	0	12	>500
Compound 34	52	86	100	<10
E-Germacrene D (**38**)	0	39	100	ca. 126
Podophyllotoxin	74	93	100	<10

EXAMPLE 5

ANTIFUNGAL ACTIVITY

The antifungal activities of compounds of the invention was determined using a plate diffusion method. Plates containing medium and a fungal species were made up and 150 microgramme aliquots of a test compound of the invention were spotted onto the plate. The diameter of inhibition of fungal growth around the test compound was then determined. The results of the tests are shown in Table 9 below.

Table 9: Antifungal Activity

	Test Microorganism		
COMPOUND	***Botryis cinerea***	***Rhizoctonia solani***	***Saprolegnia asterophora***
Aristolactam B (**3**)	-	+	-
Aristolactam C (**4**)	+	+	+ +
Eupomatenoid-7 (**7**)	-	-	-
Eupomatenoid-1 (**8**)	-	-	-
Licarin-A (**16**)	-	+ +	-
Eupomatenoid-8 (**17**)	-	-	-
Dihydrocarinatidine (**21**)	+	+	+
Coniferyl alcohol (**29**)	-	-	-
Vanillin (**31**)	-	-	-
Compound 34	+ +	+ +	+ +
E-Germacrene D (**38**)	+	-	-
- = no inhibition + = 5mm diameter inhibition + + = 5-10mm diameter inhibition			

CLAIMS

1. The use of an extract from *Aristolochia taliscana* or one or more anti-mutagenically active compounds isolable therefrom for the manufacture of a medicament for the treatment of disease states mediated by mutagenesis.

2. The use of an extract from an *Aristolochia* species such as *Aristolochia taliscana* or one or more component compounds isolable therefrom for the manufacture of a medicament for the treatment of chronic inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, synovitis and psoriasis.

3. The use of an extract from *Aristolochia taliscana* or one or more antifungally active compounds isolable therefrom for the manufacture of a composition for antifungal use, for example in the treatment of fungal infections in animals, or for use in the treatment of fungal infections in plants.

4. The use according to any one of claims 1 to 3 wherein the composition contains at least 10%, preferably at least 20%, and more preferably at least 25% by weight of a phenylbenzfuran.

5. The use according to claim 4 wherein the phenylbenzfuran is a eupomatenoid.

6. The use according to claim 4 or claim 5 wherein the phenylbenzfuran contains a phenolic group.

7. The use according to claim 6 wherein the phenylbenzfuran is eupomatenoid-7.

8. The use according to any one of the preceding claims wherein the composition contains Licarin-A.

9. The use according to any one of the preceding claims wherein the

composition contains a cytotoxic tetralone compound.

10. The use according to any one of the preceding claims wherein the composition contains a 2-hydroxy-1-tetralone compound.

11. The use according to claim 9 or claim 10 wherein the tetralone compound is (2R,4S)-2-Hydroxy-6-methoxy-4,7-dimethyl-1-tetralone.

12. The use according to any one of the preceding claims wherein the composition contains at least 25% by weight of a phenolic eupomatenoid compound (such as eupomatenoid-7), at least 8% of Licarin-A and at least 8% of a non-phenolic eupomatenoid compound (such as eupomatenoid-8).

13. The use according to any one of the preceding claims wherein the composition contains an aristolactam.

14. The use according to any one of the preceding claims wherein the extract has been prepared by extraction of plant material from the *Aristolochia* species with an organic solvent.

15. The use according to claim 14 wherein the organic solvent is an alcoholic solvent such as ethanol or methanol or a mixture thereof.

16. The use according to claim 14 wherein the organic solvent is benzene, the solvent having been removed from the extract prior to use.

17. A method of treating a disease state mediated by mutagenesis, which method comprises administering to a patient suffering from said disease state an effective antimutagenic treatment amount of an extract from an *Aristolochia* species or one or more antimutagenic compounds isolable therefrom, as defined in any one of the preceding claims.

18. A method of inhibiting mutagenesis in an organism, which method comprises administering to the organism an effective antimutagenic amount

of an extract from *Aristolochia taliscana* or one or more antimutagenic compounds isolable therefrom, as defined in any one of the preceding claims.

19. A method of producing a cytotoxic effect in an organism (such as an animal), which method comprises administering to the organism in an amount effective to produce the cytotoxic effect an extract from *Aristolochia talscana* or one or more cytotoxic compounds isolable therefrom, as defined in any one of the preceding claims.

20. A method of preventing or treating a fungal infection in an animal patient such as a human, which method comprises administering to the patient an effective antifungal amount of an extract from *Aristolochia taliscana* or one or more antifungal compounds isolable therefrom, as defined in any one of the preceding claims.

21. A method of preventing or treating a fungal infection in a plant, which method comprises administering to the plant an effective antifungal amount of an extract from *Aristolochia taliscana* or one or more antifungal compounds isolable therefrom, as defined in any one of the preceding claims.

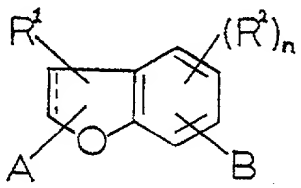
22. A method of inhibiting fungal growth in a substrate, which method comprises administering to the substrate an antifungal effective amount of an extract from *Aristolochia taliscana* or one or more antifungal compounds isolable therefrom, as defined in any one of the preceding claims.

23. A method according to claim 22 wherein the substrate is selected from animal (e.g. mammals such as humans) and plant tissues.

24. A method of treating a chronic inflammatory disease such as inflammatory bowel disease, rheumatoid arthritis, synovitis or psoriasis in a patient, which method comprises administering to the patient an effective amount of an extract from an *Aristolochia* species such as *Aristolochia taliscana* or one or

more component compounds isolable therefrom.

25. The use of a compound for the manufacture of a medicament for use in any one or more of the therapeutic uses selected from the treatment of neoplastic diseases or diseases mediated or initiated by mutagenesis or abnormal cellular proliferation, or as a cytotoxic agent, or the treatment of chronic inflammatory conditions, the compound being of the formula (I):



(I)

wherein the dotted line signifies a single or double bond; n is 0, 1, 2 or 3; A is a monocyclic aryl ring optionally substituted by one or more substituent groups which may be the same or different and are selected from R^3O, R^3, R^3S, halogen; aryl and heteroaryl, wherein R^3 is hydrogen, or a hydrocarbyl group optionally substituted by a hydroxy or hydrocarbyloxy group; B is selected from carboxy, carboxaldehyde, hydrocarbyl and hydrocarbyloxy groups wherein the hydrocarbyl group is acyclic or cyclic, and optionally contains one or more heteroatoms, and is optionally substituted by one or more hydroxy, alkoxy, alkenyloxy, alkynyloxy, aryloxy, aldehyde, alkanoyl, acetal, hemiacetal and carboxy groups; R^1 is hydrogen or a hydrocarbyl group optionally including one or more heteroatoms and optionally substituted by one or more substituents selected from hydroxy, hydrocarbyloxy and aryl groups; and R^2 is hydroxy or a hydrocarbyl or hydrocarbyloxy group optionally substituted by one or more substituents selected from hydroxy, hydrocarbyloxy and aryl groups.

26. The use according to claim 25 wherein the monocyclic aryl ring A is attached to the 2-position of the furan ring.

27. The use according to claim 25 or claim 26 wherein the aryl ring is a phenyl group.

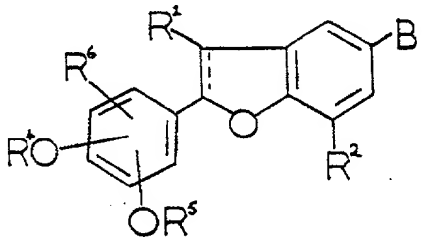
28. The use according to any one of claims 25 to 27 wherein the group B is attached to the 5-position of the benzofuran group.

29. The use according to any one of claims 25 to 28 wherein there is only one group R^2.

30. The use according to claim 29 wherein the group R^2 is attached to the 7-position of the benzofuran ring.

31. The use according to any one of claims 25 to 30 wherein the dotted line signifies a double bond.

32. The use according to claim 25 wherein the compound of the formula (I) has the formula (II):



(II)

wherein B, R^1 and R^2 are as defined in any one of claims 25 to 31, R^4 and R^5 are the same or different and each is selected from hydrogen, C_{1-20} hydrocarbyl, C_{5-20} aryl, or C_{5-20} oxygen-containing heteroaryl; R^6 is selected from hydrogen, halogen, C_{1-20} hydrocarbyl or C_{1-20} hydrocarbyloxy optionally substituted by one or more hydroxy, alkoxy, aralkyloxy groups; or R^6 is C_{5-25} aryl or oxygen or nitrogen-containing heteroaryl.

33. The use according to claim 32 wherein B is C_{1-6} alkyl or alkenyl optionally substituted by one or more substituents selected from hydroxy, CHO, or R^7O wherein R^7 is a C_{1-6} alkyl or alkenyl group.

34. The use according to claim 33 wherein the group B is selected from $CH=CHCH_3$, $CH_2CH=CH_2$, $CH(OH)CH=CH_2$, $CH=CHCHO$, CHO, $CH=CHCH_2OH$ and $CH(OH)CH(OH)CH_3$.

35. The use according to claim 34 wherein B is $CH=CHCH_3$.

36. The use according to any one of claims 25 to 35 wherein R^4 and R^5 are selected from hydrogen, or C_{1-6} alkyl, or R^4 and R^5 together define an alkylene group such as $-CH_2-$.

37. The use according to claim 36 wherein at least one of R^4 and R^5 is hydrogen.

38. The use according to any one of claims 32 to 37 wherein R^6 is selected from hydrogen, halogen, C_{1-6} alkoxy (e.g.methoxy), a 2-benzofuranyl ring, and an aristolactam group.

39. The use according to any one of claims 25 to 38 wherein each hydrocarbyl group is selected from aliphatic, alicyclic and aromatic groups.

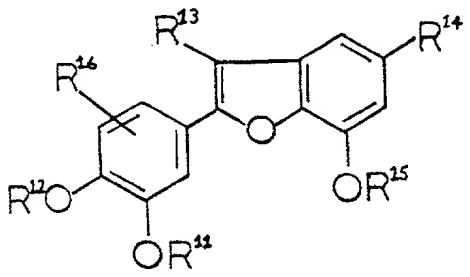
40. The use according to claim 39 wherein the hydrocarbyl group is selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, aryl, aralkyl, aralkenyl, aralkynyl, optionally interrupted by one or more heteroatoms such as oxygen and sulphur.

41. The use according to claim 40 wherein the hydrocarbyl group is a C_{1-6} alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl; a cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicycloheptanyl, decalinyl, adamantyl, norbornyl and bicyclooctyl; an alkenyl or alkynyl groups selected from vinyl, ethynyl, allyl, 1-propenyl, propargyl, but-1-enyl, but-2-enyl, but-3-enyl and 3-methylbutenyl; a cycloalkenyl group selected from cyclopentenyl, cyclohexenyl and cycloheptenyl; an aryl groups selected from phenyl and naphthyl; or a phenylalkyl or phenylalkenyl groups selected from benzyl, phenethyl, phenylpropyl, phenylbutyl and styryl groups.

42. A compound of the formula (I) or (II) as defined in any one of the preceding claims for use in medicine, for example for use in any one or more of the therapeutic uses selected from the treatment of neoplastic diseases or diseases mediated or initiated by mutagenesis or abnormal cellular proliferation, or as a cytotoxic agent, or the treatment of chronic inflammatory conditions, or as an anti-fungal agent in the treatment of fungal infections in plants or animals; but provided that when R^1 is 3-methyl, R^2 is a single methoxy group at the 7-position, and either (i) the furan ring is unsaturated and is substituted at the 2-position with a 4-hydroxy-3-methoxyphenyl group or a 3,4-methylenedioxyphenyl group; or (ii) the furan ring is a 2,3-dihydrofuran ring and is substituted at the 2-position with a 4-hydroxy-3-methoxyphenyl group, then B is other than a prop-1-enyl group attached to the 5-position of the benzfuran ring.

43. A pharmaceutical composition comprising a compound of the formula (I) or (II) as defined in claim 42 together with a pharmaceutically acceptable carrier.

44. A compound of the formula (III):



wherein R^{11} is hydrogen or C_{1-6} alkyl;

R^{12} is selected from hydrogen, C_{1-6} alkyl; a cyclic terpenoid group or a group of the formula E, G or J;

R^{13} is selected from hydrogen; C_{1-3} alkyl or hydroxy-C_{1-3} alkyl;

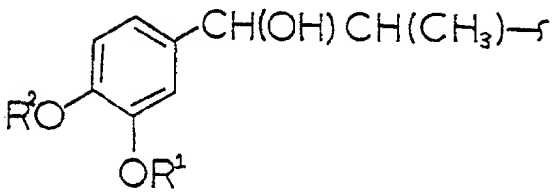
R^{14} is selected from $CH=CH\text{-}CH_3$, $CH(OH)CH=CH_2$, $CH=CH\text{-}CHO$,

CH=CH-CH_2OH, CH(OH)CH(OR^{17})CH_3, or a group L;

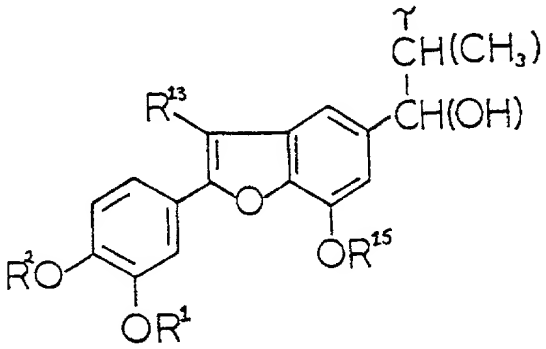
R^{15} is hydrogen or C_{1-6} alkyl;

R^{16} is hydrogen, a group M or an aristolactam group; and

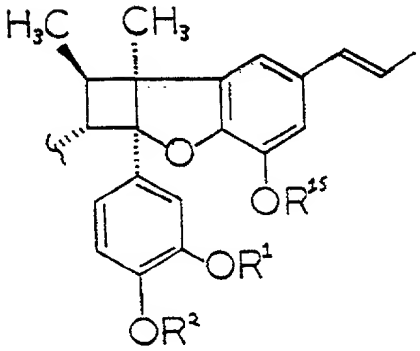
R^{17} is hydrogen or a group T; wherein the groups E, G, L, J, M and T are represented by the formulae:



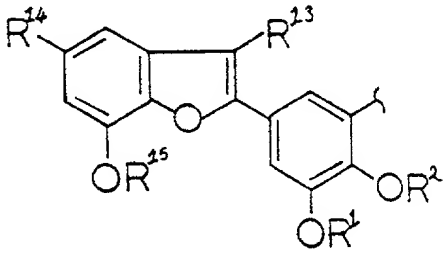
(E)



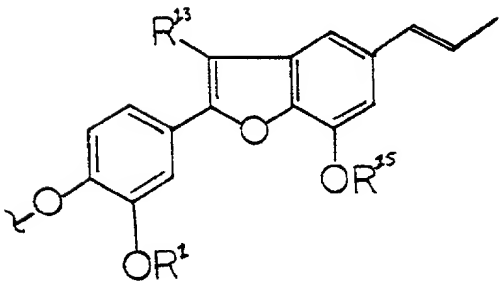
(G)



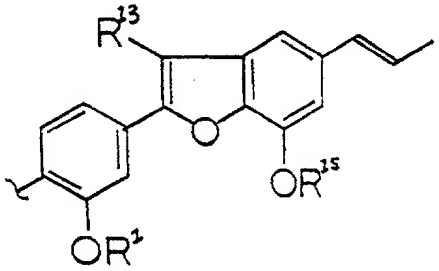
(L)



(J)



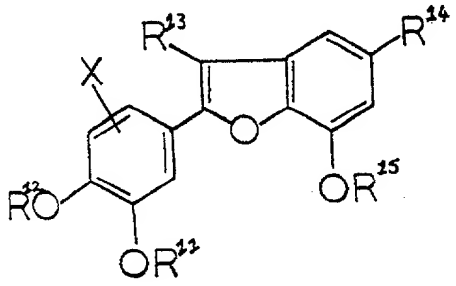
(M)



(T)

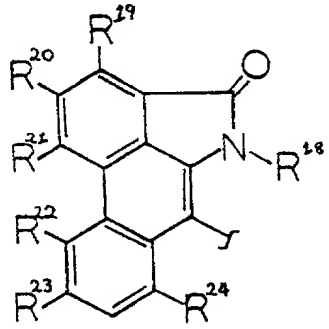
and pharmaceutically acceptable salts thereof, provided that when R^{11}, R^{13} and R^{15} are all methyl,and R^{12} and R^{16} are both hydrogen, R^{14} is selected only from $CH(OH)CH=CH_2$, $CH=CH\text{-}CHO$, $CH=CH\text{-}CH_2OH$, $CH(OH)CH(OR^{17})CH_3$ where R^{17} is a group T, or a group L.

45. A compound of the formula (IV):



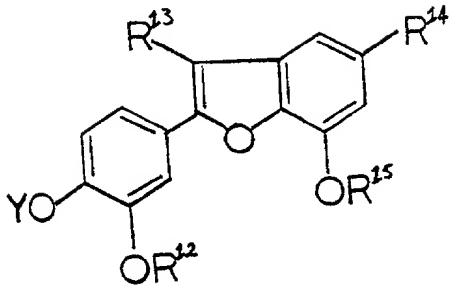
(IV)

wherein R^{11}, R^{12}, R^{13} R^{14}, R^{15} and R^{17} are as defined in claim 25 and X is a group:



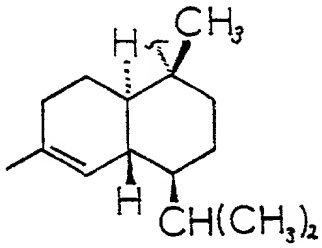
wherein R^{18} is hydrogen, benzyl or C_{1-6} alkyl; R^{19} to R^{24} are the same or different and are selected from hydrogen, hydroxy, C_{1-6} alkoxy, C_{1-6} alkyl and hydroxy-C_{1-6} alkyl; or any two adjacent groups together form an alkylene dioxy group.

46. A compound of the formula (V):

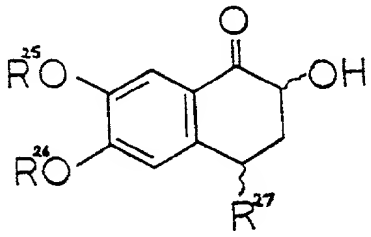


(V)

wherein Y is a monocyclic or bicyclic terpenoid group and in particular a group of the structure:



47. A tetralone compound of the formula (VI):



wherein R^{25} and R^{27} are the same or different and each is C_{1-6} alkyl; and R^{26} is hydrogen or C_{1-6} alkyl, or R^{25} and R^{26} together form an alkylene-dioxy group.

48. A compound according to claim 48 wherein R^{25}, R^{26} and R^{27} are all methyl.

49. A compound according to claim 47 or 48 for use as a biocide.

50. A compound according to claim 49 for use in the treatment of fungal infections, or for use in the treatment of cancers and other proliferative diseases such as psoriasis.

51. A compound selected from the group consisting of:
(±)-5-(1-Hydroxyallyl)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran;
2-(4-Hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-5-(E)-propenylbenzofuran;
2-(4-Hydroxy-3-methoxyphenyl)-7-methoxy-3-methyl-5-[(E)-3-oxopropenyl]benzofuran;
5-Formyl-3-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran;
2-(4-Hydroxy-2-methoxyphenyl)-5-[(E)-3-hydroxypropenyl]-7-methoxy-3-methylbenzofuran;
2-(3,4-Dihydroxyphenyl)-7-methoxy-3-methyl-5-(E)-propenylbenzofuran;
erythro-5-(1,2-Dihydroxypropyl)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran;
(2R,3R)-2,3-Dihydro-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-5-(E)-propenylbenzofuran;
erythro-1-(4-Acetoxy-3-methoxyphenyl)-2-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propylacetate;
threo-1-(4-Acetoxy-3-methoxyphenyl)-2-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propyl-acetate;
threo-1-[2-(4-Hydroxy-3-m ethoxyphenyl)-7-methoxy-3-methylbenzofuran-5-yl]-2-[4-(3-methyl-5-(e)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propan-1-ol;
2-Methoxy-4-[7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl]-6-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]phenol;
8.2',9.3'-Tetrahydro-bis-eupomatenoid-7;
15-(Aristolactam-I-9-yl)-eupomatenoid-7;
14-O-α-Cadinyl-eupomatenoid-7; and
(2R,4S)-2-Hydroxy-6-methoxy-4,7-dimethyl-1-tetralone.

52. A pharmaceutical composition comprising a compound as defined in any one claims 44 to 51 together with a pharmaceutically acceptable carrier.

ABSTRACT

The invention relates to extracs from *Aristolochia taliscana* and their uses in medicine, and also to compounds, known and novel isolated from the extracts, and composition containing the extracts and compounds. The extracts and comounds are useful *inter alia* as anti-mutagens, antifungal agents and cytotoxic agents. The extracts and compositions of the invention can comprise at least 10%, preferably at least 20%, and more preferably at least 25% by weight of a phenylbenzfuran.

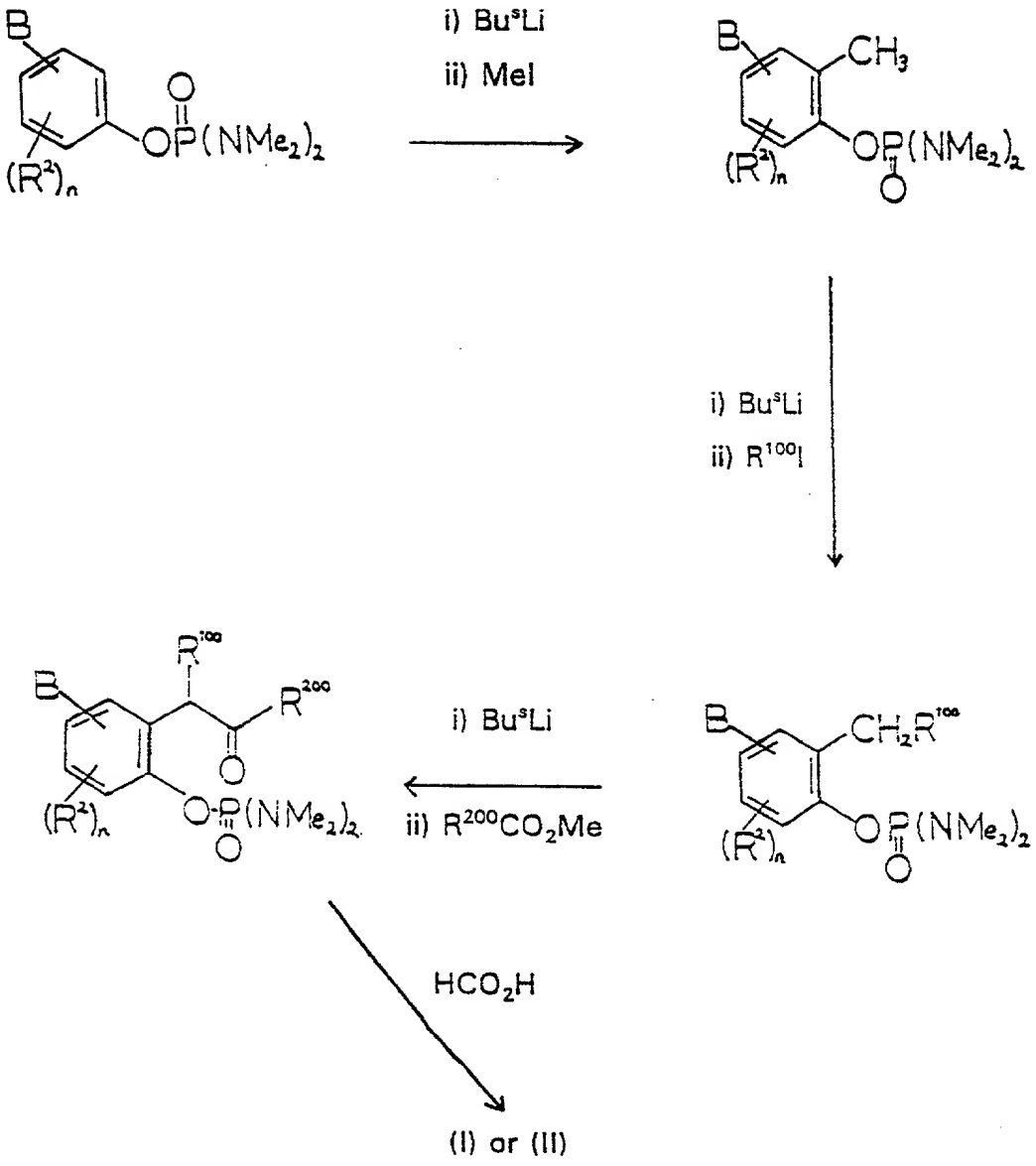

i) Bu^{s}Li
ii) MeI
i) Bu^{s}Li
ii) R^{100}I
i) Bu^{s}Li
ii) R^{200}CO$_2$Me
HCO$_2$H
(I) or (II)

Figure 1

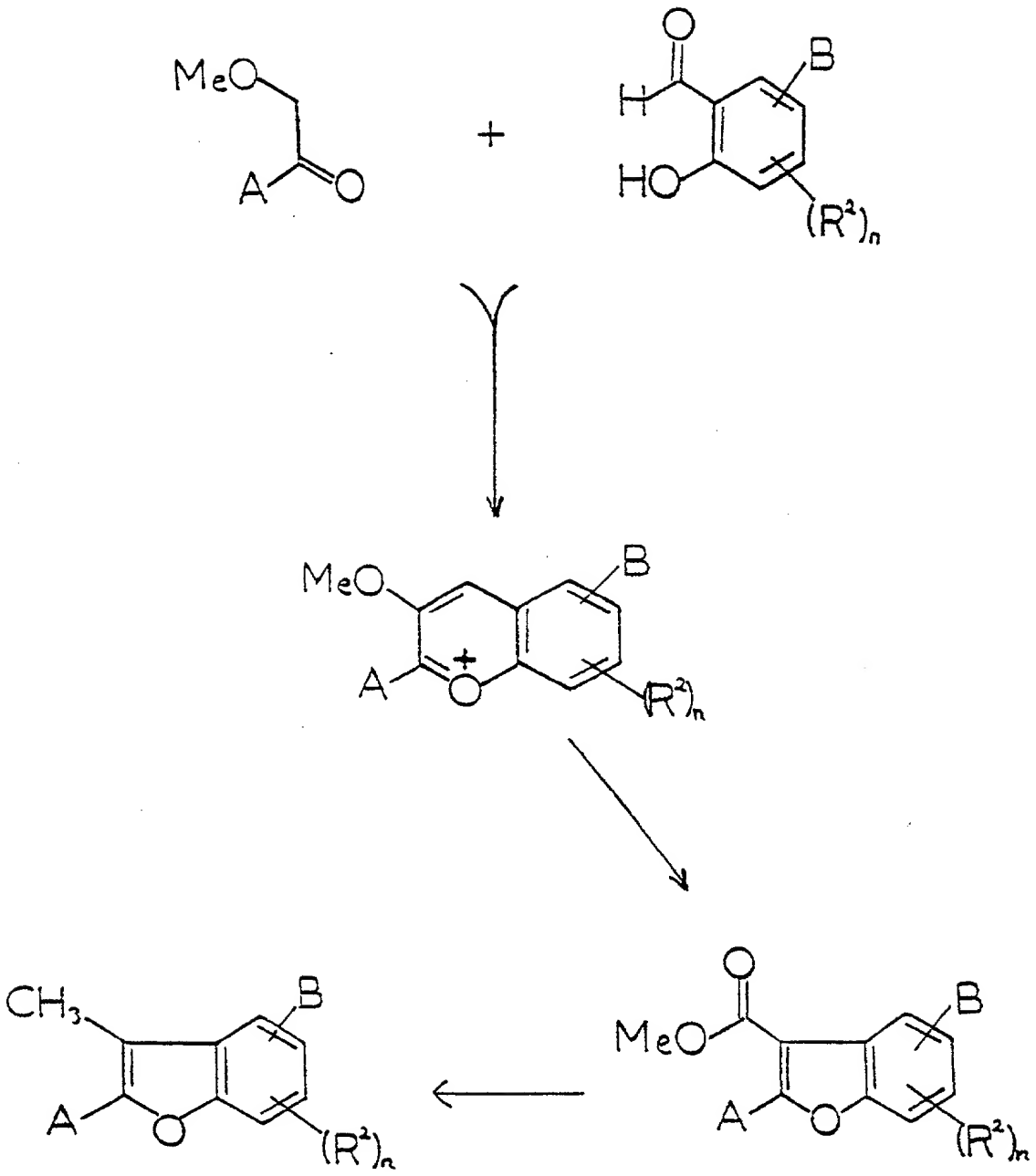


Figure 2

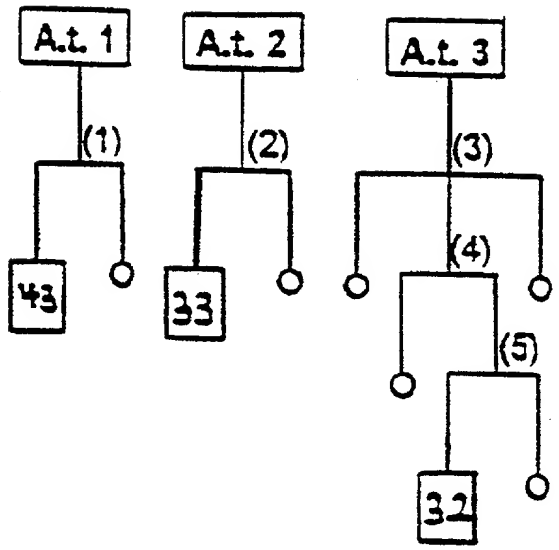
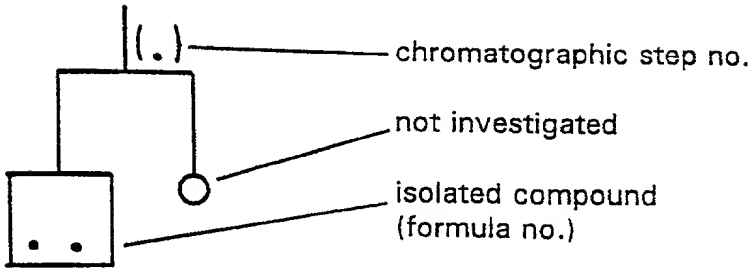


Figure 3

KEY TO DIAGRAMS



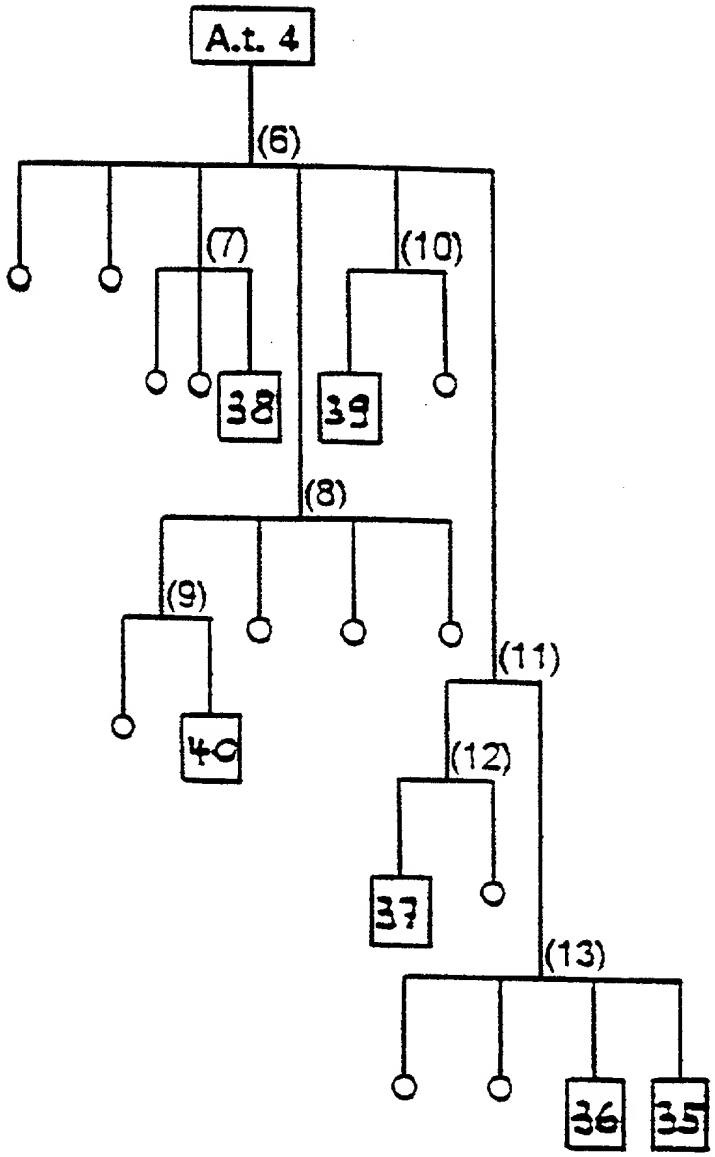


Figure 3 Continued

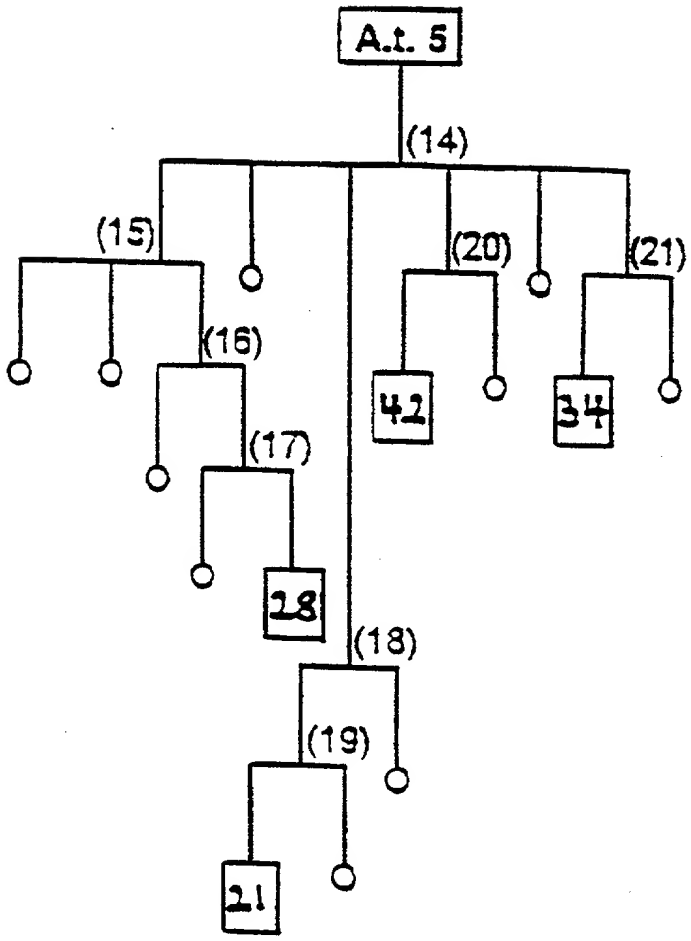


Figure 3 Continued

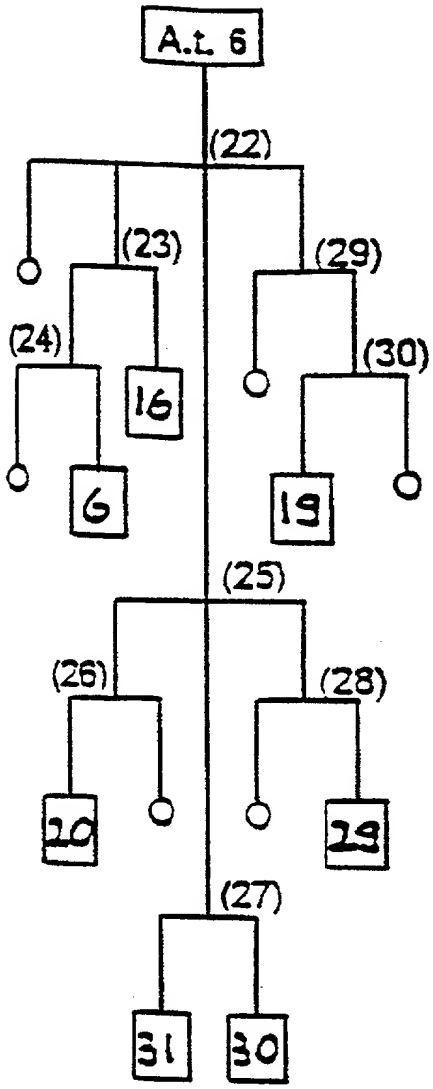


Figure 3 Continued

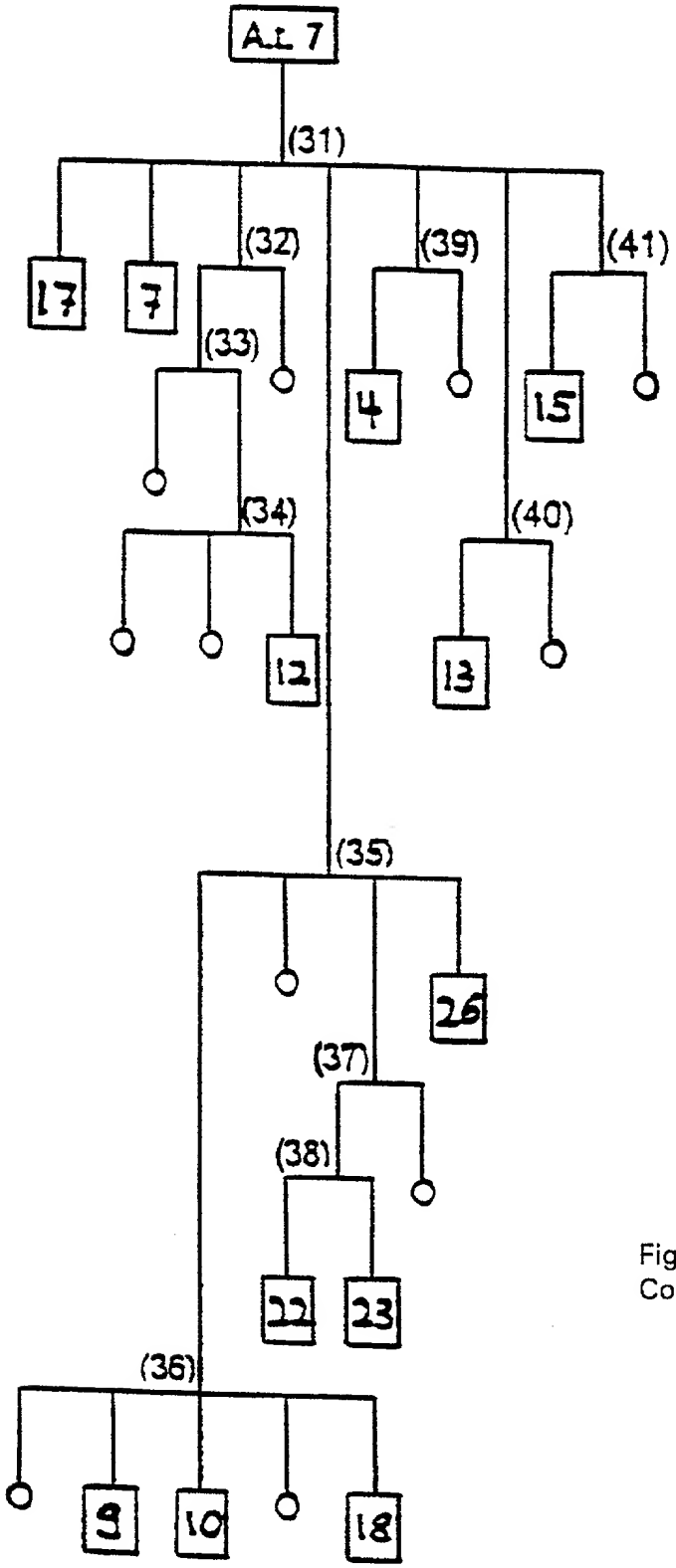


Figure 3
Continued

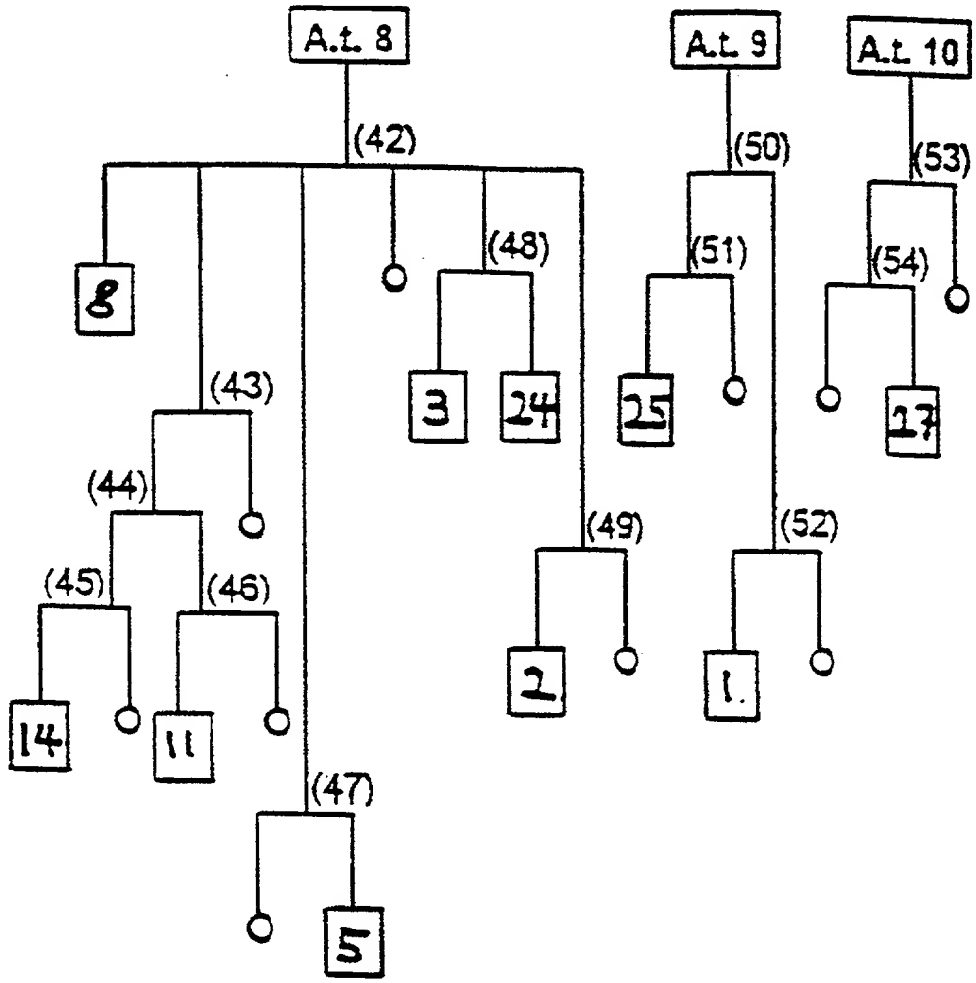


Figure 3 Continued

COMBINED DECLARATION AND POWER OF ATTORNEY

(Original, Design, National Stage of PCT, Divisional, Continuation or C-I-P Application)

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PHARMACEUTICAL COMPOUNDS ISOLATED FROM ARISTOLOCHIA TALISCANA

This declaration is of the following type:

[] original
[] design
[X] national stage of PCT.
[] divisional
[] continuation
[] continuation-in-part (C-I-P)

the specification of which: *(complete (a), (b), or (c))*

(a) [ ] is attached hereto.
(b) [X] was filed on January 31, 2000 as Application Serial No. 09/463,851 and was amended on *(if applicable)*.
(c) [X] was described and claimed in PCT International Application No. PCT/GB98/02317 filed July 31, 1998 on and was amended on *(if applicable)*.

Acknowledgement of Review of Papers and Duty of Candor

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of the subject matter claimed in this application in accordance with Title 37, Code of Federal Regulations § 1.56.

[ ] In compliance with this duty there is attached an information disclosure statement. 37 CFR 1.98.

Priority Claim

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT International Application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT International Application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application on which priority is claimed

(complete (d) or (e))

(d) [] no such applications have been filed.
(e) [X] such applications have been filed as follows:

PRIOR FOREIGN/PCT APPLICATION(S) FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION				
COUNTRY	APPLICATION NO.	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
GB	9716244.0	31 July 1997		[X] YES NO []
				[] YES NO []
				[] YES NO []
ALL FOREIGN APPLICATION(S), IF ANY, FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION				
				[] YES NO []
				[] YES NO []
				[] YES NO []

Claim for Benefit of Prior U.S. Provisional Application(s)

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

Provisional Application Number	Filing Date

Claim for Benefit of Earlier U.S./PCT Application(s) under 35 U.S.C. 120

(complete this part only if this is a divisional, continuation or C-I-P application)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose information as defined in Title 37, Code of Federal Regulations, § 1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

(Application Serial No.) (Filing Date) (Status) (patented, pending, abandoned)

(Application Serial No.) (Filing Date) (Status) (patented, pending, abandoned)

Power of Attorney

As a named inventor, I hereby appoint Dana M. Raymond, Reg. No. 18,540; Frederick C. Carver, Reg. No. 17,021; Francis J. Hone, Reg. No. 18,662; Joseph D. Garon, Reg. No. 20,420; Arthur S. Tenser, Reg. No. 18,839; Ronald B. Hildreth, Reg. No. 19,498; Thomas R. Nesbitt, Jr., Reg. No. 22,075; Robert Neuner, Reg. No. 24,316; Richard G. Berkley, Reg. No. 25,465; Richard S. Clark, Reg. No. 26,154; Bradley B. Geist, Reg. No. 27,551; James J. Maune, Reg. No. 26,946; John D. Murnane, Reg. No. 29,836; Henry Tang, Reg. No. 29,705; Robert C. Scheinfeld, Reg. No. 31,300; John A. Fogarty, Jr., Reg. No. 22,348; Louis S. Sorell, Reg. No. 32,439; Rochelle K. Seide Reg. No. 32,300; Gary M. Butter, Reg. No. 33,841; Marta E. Delsignore, Reg. No. 32,689; Lisa B. Kole, Reg. No. 35,225; and Lindsay S. Adams, Reg. No. 36,425of the firm of BAKER BOTTS L.L.P., with offices at 30 Rockefeller Plaza, New York, New York 10112, as attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith

SEND CORRESPONDENCE TO:	DIRECT TELEPHONE CALLS TO:
BAKER BOTTS L.L.P. 30 ROCKEFELLER PLAZA, NEW YORK, N.Y. 10112 CUSTOMER NUMBER: 21003	BAKER BOTTS L.L.P. (212) 705-5000

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

FULL NAME OF SOLE OR FIRST INVENTOR	LAST NAME ACHENBACH	FIRST NAME HANS	MIDDLE NAME	
RESIDENCE & CITIZENSHIP	CITY Wiesbaden	STATE or FOREIGN COUNTRY Germany DEX	COUNTRY OF CITIZENSHIP Germany	
POST OFFICE ADDRESS	POST OFFICE ADDRESS Am Rheineck 7	CITY Wiesbaden	STATE or COUNTRY Germany	ZIP CODE D65199
DATE 28-05-2000	SIGNATURE OF INVENTOR Dr. H. Achenbach			
FULL NAME OF SECOND JOINT INVENTOR, IF ANY	LAST NAME	FIRST NAME	MIDDLE NAME	
RESIDENCE & CITIZENSHIP	CITY	STATE or FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP	
POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE or COUNTRY	ZIP CODE
DATE	SIGNATURE OF INVENTOR			
FULL NAME OF FOURTH JOINT INVENTOR, IF ANY	LAST NAME	FIRST NAME	MIDDLE NAME	
RESIDENCE & CITIZENSHIP	CITY	STATE or FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP	
POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE or COUNTRY	ZIP CODE
DATE	SIGNATURE OF INVENTOR			

Check proper box(es) for any added page(s) forming a part of this declaration

[ ] Signature for ninth and subsequent joint inventors. Number of pages added _____.

[ ] Signature by administrator(trix), executor(trix) or legal representative for deceased or incapacitated inventor. Number of pages added _____.

[ ] Signature for inventor who refuses to sign, or cannot be reached, by person authorized under 37 CFR 1.47. Number of pages added _____.